THE 1942 YEAR BOOK *of* GENERAL MEDICINE

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DEPARTMENTS *of the* YEAR BOOK *of* GENERAL MEDICINE

Infectious Diseases

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Diseases of the Chest

(Exc pting the He rt)

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Diseases of the Blood and Blood Forming Organs
Diseases of the Kidney

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Diseases of the Heart and Blood Vessels

WILLIAM D STROUD MD

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Un e s ty of P n ylv

Dis ases of the Digestive System and of Metabolism

GEORGE B EUSTERMAN MD

P fe f Med in U s ty f M t (M yo Fo d ti n)
Se a Co s lt nt Med e M yo Cl ic

This volume is one of the 12 comprising the Practical Medicine Series of Year Books founded in 1900 by G P Head M D and C J Head and published continuously since then The complete list follows

General Medicine *Infectious Diseases* edited by GEORGE F DICK M D *Diseases of the Chest* by J BURNS AMBERSON JR M D *Diseases of the Blood Blood Forming Organs and Kidney* by GEORGE R MINOT M D and WILLIAM B CASTLE M D *Diseases of the Heart and Blood Vessels* by WILLIAM D STROUD M D *Diseases of the Digestive System and of Metabolism* by GEORGE B EUSTERMAN M D

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GEORGE F DICK MD

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GEORGE F DICK MD

GENERAL MEDICINE

PART I

INFECTIOUS DISEASES

In reviewing the literature on infectious diseases for the past year special attention has been paid to work bearing on war medicine including tropical diseases —Ed

ANTHRAX

Cutaneous Anthrax Treated by Arsenicals and Sulfapyridine is reported by Ian Mackenzie Davidson[1]

Man 53 was hospitalized January 25 A week before he noted a small pimple on the back of his neck simulating an early boil The evening before admission the pimple quickly extended and the surrounding area swelled rapidly During the next 24 hours the swelling extended to each side of the neck *and vomiting occurred.*

Examination revealed a blood stained vesicular lesion about 1 in in diameter The vesicle was not tense and the overlying cuticle was crenated There was solid edema of the surrounding parts extending to the interscapular region occiput and lateral aspect of the neck in front of the sternocleido mastoids Temperature was 102 4 F and pulse rate 108 Tongue was moist but slightly furred The mouth heart lungs spleen and urine were negative

Smears of fluid from the lesion showed gram positive cocci and gram negative bacilli in abundance and a few rod shaped gram positive organisms Culture after 12 hours showed the typical dried cotton wool appearance of anthrax and stained slide from culture were typical of anthrax bacillus

On January 26 sulfapyridine was started with a 2 Gm initial dose followed by 1 Gm every 4 hours for 48 hours then 1 Gm three times daily for 36 hours Later 0 5 Gm was given three times daily for four days total dosage being 24 5 Gm The day after admission 10 cc of Sclavo s anti anthrax serum was given subcutaneously into the abdominal wall Arsenic was also given intravenously in the form of

(1) B M J 725 7 6 N 1941

neokharsivan in doses of 0 6 Gm on the second, third and sixth days after admission Leukocyte counts on the second, fourth and sixth days were 11,000, 16,800 and 9,200, respectively

The condition of the lesion had not markedly altered on January 27 but temperature and pulse rate were normal and remained so until dismissal

By January 30 the patient looked and felt much better The edema had largely subsided the original lesion being a bluish black scab the edges of which were beginning to separate Below the original lesion was a large, flat blood stained blister containing gelatinous sanious material Cultures from scar and blister at this stage yielded abundant growths of Staphylococcus aureus but both were negative for Bacillus anthracis By February 2 the original lesion was still drier The central eschar was further separated and was surrounded by a pale, slightly raised ring

The patient was discharged February 7 There was only slight residual induration from the occiput to the interscapular region behind and the dry scab had almost completely separated, exposing a healed eschar The blood blister had disappeared When seen one month later he was quite well

Diagnosis of anthrax was confirmed by inoculation of a guinea pig which died within 48 hours, the heart blood and spleen giving cultures positive for anthrax

[It is impossible to state which of the measures used was responsible for recovery in this case of anthrax —Ed]

ARTHRITIS

Evaluation of Medical Treatment in Rheumatoid Arthritis According to Guy W Carlson[7] (Appleton), focal infection is only an influencing factor in rheumatoid arthritis and as such its eradication cannot be considered curative Foci are better eradicated early than late but such removal is seldom effective The value of autogenous vaccines is improved Use of small descending doses gives best results and early cases are best suited for vaccine treatment When given correctly and used with other proved forms of therapy, vaccines will be more effective

Sulfur therapy has been generally discarded Cold

(7) W[illegible] M J 41 [illegible] [illegible] 194[illegible]

salts have distinct therapeutic value but toxic reactions are a serious disadvantage The most severe toxic reactions have occurred in patients with normal sedimentation rates or when the rate has been below 12 mm Careful dosage guided by frequent study of sedimentation rates may eliminate the serious objections to gold therapy Bee venom is not specific but is of value in selected cases Chaulmoogra oil is irritating painful and of questionable value Vitamin deficiency according to Haden is not the cause of the disease but may be an influencing factor Hence the indication for diets adequate in vitamins

A cardinal principle in treatment is that the patient be treated as a whole A carefully planned medical program guided by a complete history and physical and laboratory examinations continues to be the best regimen

[This is a concise statement of the status of therapy in rheumatoid arthritis We do not believe that vaccines are of sufficient value to warrant their use —Ed]

Gold Salts in Treatment of Rheumatoid Arthritis Study of 245 Cases Russell L Cecil William H Kammerer and Francois J DePrume[3] (Cornell Univ) observed remission or marked improvement in 62 per cent of patients treated with adequate doses of gold salts Of 10 patients with ankylosing spondylitis gold salts were beneficial in only 1 Best results were obtained in patients with arthritis of less than one year s duration

Incidence of toxic reactions was high These were manifested chiefly as dermatitis or stomatitis There was one fatal case of ulcerative enteritis which may possibly have been due to the gold salts Relapses occurred in 42 per cent of the patients who received marked benefit from gold therapy The relapses were usually milder than the original attack but yielded less promptly to gold therapy

[We have been more impressed with the dang rs than with the value of gold therapy —Ed]

(3) A I t M d 16 811 8 7 M y 194

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( ) Wisc M J 41 4 43 Ja y 194

Clinical Manifestations and Diagnosis of Chronic Brucellosis Robert C Manchester[5] (Alliance O) states that brucellosis should be recognized as a chronic sys temic infection capable of persisting through many years of a patient s life Constant reinfection may be a factor for in many cases exposure continues un checked Clinical manifestations are variable Never theless *various combinations of protracted fever chronic* fatigue and nervousness recurrent griplike attacks characteristically with prolonged convalescence head ache palpitation gastro intestinal complaints joint pains and myalgias should suggest chronic brucellosis

Of 100 patients with chronic complaints 38 gave positive reactions to the intradermal test for brucella Joint manifestations consisted of arthralgias pain and stiffness in the involved joints and frequently moderate swelling No redness was observed Characteristically there was absence of residual deformity or permanent impairment of function No relationship was found between brucellosis and rheumatoid arthritis in the cases observed A normal sedimentation rate aids in differentiating active phases of rheumatoid arthritis from brucellosis In this series the intradermal test was a reliable index of brucella infection Only one patient with a negative skin test presented a clinical picture compatible with brucellosis It is to be empha sized that neither the skin test nor the severity of the local or general reaction gives reliable information as to whether the infection is active or latent

Contagious Abortion of Cattle and Undulant Fever in Man, as they exist in Western Canada are discussed by J S Fulton[6] (Univ of Saskatchewan) Surveys conducted in the Saskatchewan area revealed that the average percentage of infected cows located from 1933

(5) A I t M d 16 950 965 M y 194
(6) M Offi 55 01 20 J 21 1941

Roentgen Therapy for Rheumatoid Arthritis of the Spine C J Smyth R H Freyberg and Isadore Lampe[4] (Univ of Michigan) treated 52 patients with typical rheumatoid arthritis of the spine with local high voltage roentgen radiation Thirty seven were significantly improved with reference to symptoms and 26 were significantly improved as judged by physical findings Results were excellent in patients with early disease in whom roentgenograms revealed abnormalities only in the sacro iliac joint in this group 92 per cent showed significant sustained subjective and objective improvement and some were completely relieved of all clinical evidence of the disease In the later stages after spinal ligamentous calcification had occurred it was found that a high percentage showed significant reduction in pain and stiffness and some showed objective improvement No evidence was found for a psychogenic basis for symptomatic relief

The erythrocyte sedimentation rate decreased significantly after roentgen therapy in 41 per cent Leukopenia was found in three patients but all recovered completely within one month after therapy The possible occurrence of leukopenia with roentgen therapy emphasizes the necessity for frequent blood counts to avoid serious sequelae

(4) J A M A 117 6831 Sept 6 1941

BRUCELLOSIS

Clinical Manifestations and Diagnosis of Chronic Brucellosis Robert C Manchester[5] (Alliance O) states that brucellosis should be recognized as a chronic systemic infection capable of persisting through many years of a patient s life Constant reinfection may be a factor for in many cases exposure continues unchecked Clinical manifestations are variable Nevertheless various combinations of protracted fever chronic fatigue and nervousness recurrent griplike attacks characteristically with prolonged convalescence headache palpitation gastro intestinal complaints joint pains and myalgias should suggest chronic brucellosis

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(6) M Offic 55 01 20 J 1 1941

to 1939 was 5 68 while during 1938 and 1939 this was reduced to 2 68 In the same periods the percentage of infected humans located has fallen from 4 34 to 2 11 The decided reduction in percentage of reactors is perhaps due to the annual testing of dairy herds in certain districts where such is compulsory before milk may be sold In addition stock owners are aware of the danger of harboring infected animals and seldom do so

Fulton considers partial reactions as an indication of the disease The significance of partial reactions may be difficult to determine particularly when the patient s symptoms are ill defined To ascertain the validity of partial reactions a number of experimental animals were inoculated with live cultures of Brucella abortus and a like number were given suspensions of the organisms which had been destroyed by heating Agglutination tests conducted periodically showed that those receiving live organisms reacted positively to high dilutions in some instances for over a year The titers of serums from animals inoculated with dead cultures were at first quite comparable to those in the other group but rapidly fell and in some cases completely disappeared in a few months At the end of the experiment animals which had received the live organism were destroyed and examined for Brucella abortus Those giving even a partial reaction usually harbored the organism If these results apply to human infections a positive or partial result suggests active infection

The milk of 60 positive reacting animals was cultured and examined for Brucella abortus The organism was isolated from 70 per cent Brucella abortus will survive for at least 18 months in sterilized milk when refrigerated it has been recovered after 10 months from milk kept at room temperature in the dark

Treatment of Brucellosis by Use of Sulfaguanidine Ewart S Sarvis (Sumas Wash) reports three cases

[illegible]

in which apparent cure resulted from use of sulfaguanidine. An illustrative case is presented here.

Man, 31, was admitted with a positive diagnosis of brucellosis. Maximum temperature ranged from 101 to 103 F. for a month following admission. Treatment with sulfaguanidine was thereupon started with dosage 9 Gm. daily for three days, then 3 Gm. daily. Temperature remained normal from the third day onward. Recovery was uneventful.

Study of Fatal Case of Brucellosis is presented by Raul Tovar Mancera[8] (Mexico City).

Woman, 33, with proved chronic brucellosis of 27 months' duration died with manifestations of encephalitis, hemorrhagic purpura and ulcerative dermatitis. At autopsy no lesions of the central nervous system could be found except congestion of the pia. The main pathologic findings were: generalized sepsis, verrucous endocarditis, erofibrinous pericarditis, myocarditis, splenomegaly, pleural infarcts, chronic interstitial hepatitis, subacute glomerulonephritis, chronic interstitial nephritis, sclerosis of the pancreas, hemorrhagic purpura and degeneration of the adrenal cortex. Brucella melitensis was isolated on culture from endocardium, kidney and sternal marrow.

It is concluded that brucella is capable of producing lesions in all organic tissues. The lesions most frequently encountered may be grouped under four headings: inflammatory, hyperplastic, hemorrhagic and degenerative. The organic lesions probably are related to the virulence of the organism and tissue allergy of the patient. Judging by bacteriologic findings the lesions in the author's case were probably caused by the brucella itself. The inflammatory lesions of brucellosis present no characteristics which would differentiate them from other inflammatory changes. The clinical polymorphism of brucellosis is no doubt the result of the multiplicity of lesions produced by the micro-organism.

Brucellosis with Positive Blood Cultures and Negative Allergic Skin Tests. M. L. Singewald[9] reports two cases, one of which is given here.

(8) Med. ... 3:1-47, Feb. 10, 1944.
(9) New York State J. Med. 41:1766 1,6, Sept. 1, 1943.

Girl 7 who had consumed raw milk for some time was hospitalized October 13 having been taken ill seven days before with chills general *malaise* with flushing, nausea and vomiting and fever 102 105 F On admission *temperature* was *103* F pulse rate *120* respirations 20, blood pressure, 110/80 Examination revealed *the* child to be in no acute distress Aside from an enlarged, palpable spleen and an apical systolic murmur physical examination was negative

Laboratory examination showed hemoglobin *91* per cent erythrocyte 4 750 000, leukocytes 4 700, polymorphonuclears 68 per cent small lymphocytes, 25 per cent, large lymphocytes 4 per cent monocytes 5 per cent smear, negative *Widal and heterophil antibody agglutinations* were negative Stool culture was negative for organisms of the enteric disease group *Serum* showed agglutination with Brucella abortus in 1 40 dilution The allergic *skin* test with *brucellergen* (Huddleson) at *24 hours showed* an *erythema* of 2 5 cm diameter with slight elevation the test was negative after 48 hour Blood *culture* revealed Brucella abortus

Temperature remained undulatory Sulfanilamide was given without apparent effect total leukocyte count dropped to 2 900 with 48 per cent polymorphonuclears, so the sulfanilamide was stopped after the patient had received 15 8 Gm *Temperature* slowly *dropped to normal and the patient* was discharged October 31 The agglutination titer with Brucella abortus rose to 1 *320 on* October 30 and when the patient was next seen on November 15 she was apparently well and the *agglutination* reaction was negative

It is thus *demonstrated* that the *allergic* skin *test* may be negative at 48 hours even though active infection exists and that the 24 hour reactions though slight may have some significance

Brucella Endocarditis of Congenital Bicuspid Aortic Valve was observed in a case reported by *Harry F Wechsler and Einar G Gustafson*[1] *(Lenox Hill Hosp New York City)*

Farm worker, 28 had a history of slight *dyspnea on moderate* exertion of 12 year *duration* and recurrent attacks of pharyngitis associated with chills fever anasarca oliguria and frequency *of urination of two months duration* Temperature was 104 F respirations 28 pulse 90 He appeared acutely and chronically ill There was generalized cardiac enlargement with systolic and diastolic murmurs at both base

(1) Ann Int Med 16 1 51 22 J n 194

and apex There were splenomegaly hepatomegaly and slight clubbing of the nail bed but no evidence of jaundice cyanosis or petechiae Laboratory examination revealed albuminuria, microscopic hematuria numerous hyaline casts and increased erythrocyte sedimentation rate Blood cultures on routine agar mediums showed no growth

Ten days after admission agglutination tests for Brucella melitensis were positive Chills and fever to 104 F continued Two weeks after admission tenderness of nail beds was noted for the first time and shortly thereafter innumerable petechiae appeared over the entire body including the fundi and oral passages Stool examinations now gave a positive benzidine reaction Blood cultures incubated in a carbon dioxide atmosphere were positive for Brucella abortus and the opsonocytophagic reaction was markedly positive The course was unchanged and he died suddenly 36 days after admission Autopsy revealed perforating vegetative endocarditis congenital bicuspid aortic valve and abscess formation in various viscera especially the kidneys

Coexistence of Brucella Infection and Hodgkin s Disease in 14 consecutive cases is reported by N Bowman Wise and Mary A Poston[2] (Duke Univ) The obvious question may be raised whether isolation of this organism from patients with Hodgkin s disease represents merely latent brucella infection or is of etiologic significance Most of the patients were natives of an area in which brucella infection is widespread but if they had merely a latent infection peculiar to this region positive cultures would be expected with equal frequency in other patients with chronic diseases of the lymphatic system Such has not been the case On repeated study of a much larger group of patients with lymphosarcoma leukemia tuberculous adenitis and the like brucella was isolated only once from cultures of 67 lymph nodes and repeated blood cultures were negative with one exception In the 14 cases of Hodgkin s disease cultures yielding brucella were obtained with the greatest frequency when the disease was actively progressing rather than when it was subacute or temporarily arrested

(2) J A M A 115 19 6 1984 Dec 1940

Sufficient correlation was found between the cultural and immunologic manifestations and the clinical course of these patients to justify the belief that the brucella infection directly influences the syndrome of Hodgkin's disease. The frequent lack of all evidence of an immune response when brucella could be isolated from blood cultures during recurrences of Hodgkin's disease was striking. Maximum clinical improvement in the cases coincided with the presence of serum agglutinins and significant degrees of phagocytosis for brucella.

Although the reported observations suggest the possible etiologic importance of brucella in Hodgkin's disease, the rigid postulates of Koch have not been fulfilled.

Treatment of these 14 patients was directed primarily toward the existing brucella infection as a further means of studying the influence of the infection on the course of Hodgkin's disease. A definite and often striking decrease in the size of the enlarged lymph nodes was observed after administration of sulfanilamide or sulfapyridine. The effectiveness of immune serums was not demonstrated.

DENGUE

Dengue. Francisco Ruiz Sanchez[3] states that in the epidemic of 1941 which occurred in the northwest part of the Mexican coast, 90 per cent of the population of the city of Culiacan was affected; no deaths were reported. The virus is known to pass all filters, to resist stains, formol, Lugol's solution and alcohol, to be neutralized by fatty acids and to be destroyed by concentrated solutions of bile, by manganese and quinine. The mosquito vector, Aedes aegypti, after biting the patient remains infective for 8 to 14 days. The female deposits her eggs in discarded household vessels in which small

(3) Medicina México 104 118 ... 25 194

amounts of water have accumulated Average incubation period of the disease is five days The clinical course is characterized by *an initial febrile period lasting 3-4* days violent headache intense muscular pain bradycardia and leukopenia followed by complete remission for 24 to 48 hours and a second febrile period with *return of symptoms and appearance of a rubeolaform or* scarlatiniform eruption lasting 2 3 days Complications are exceedingly rare Treatment is symptomatic The sulfonamides (3-4 Gm daily) seem to arrest or attenuate the course The acquired immunity is brief

Prophylaxis against dengue is closely correlated with that against yellow fever which may be transmitted by the same vector and consists in the customary precautions against mosquito bites and elimination of potential breeding places for larvae by destroying unused containers sealing water tanks etc or drinking chlorinated water

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DIPHTHERIA

Sulfapyridine as Aid to Postoperative Treatment of Laryngeal Diphtheria Associated with Measles Prognosis for measles associated with diphtheria is grave especially if it invades the larynx necessitating tracheotomy for relief of obstruction Most patients die of bronchopneumonia but encouraging results in treatment of measles and its complications with sulfapyridine led D F Johnstone* (Plymouth) to try such therapy in four cases with recovery in all A typical case is given here

*Girl 2 was admitted with diagnosis of measles and broncho*pneumonia The rash was first noted four days previously Temperature was 102 F pulse 150 and respirations 60 She had a croupy cough hoarseness and well marked stridor There was slight recession but no cyanosis or acute distress and the trunk and face showed a fading morbilliform rash The throat was congested but clean There were coarse rales

over both sides of the chest but no localized dulness Diagnosis was measles bronchopneumonia and possible laryngeal diphtheria Paraldehyde 2 drachms per rectum 28,000 units diphtheria antitoxin intramuscularly and oxygen by oropharyngeal intubation were given In addition she received 1 Gm sulfapyridine orally followed by 0 5 Gm every four hours Two hours later general condition was fairly good but stridor was more pronounced and she was still rather restless Luminal 1 gr was given and she was placed in a steam tent and in four hours stridor had diminished and color was still satisfactory The next day she felt much better and was sitting up in bed playing There was still some stridor and chest signs were the same as on admission Temperature was 99.4 F pulse 130 respirations 32

The second day there was little stridor but slight cyanosis was present and she was drowsy Sulfapyridine was accordingly reduced to 0 5 Gm every six hours Temperature was normal but pulse was 130 and respirations 30

Three days after admission general condition was much worse Recession and stridor had reappeared there was cyanosis and the chest was full of coarse rales Sulfapyridine 0 5 Gm was again given every four hours The general condition grew steadily worse and all physical signs of progressing respiratory obstruction were present so that at 2 00 p m tracheotomy was performed This gave immediate relief resulting in rapid improvement of color and general condition Sulfapyridine 0 5 Gm every four hours was continued until the tube was removed three days later, and shortly thereafter chest signs disappeared The wound healed rapidly and the patient was discharged 5[1] weeks after admission

[The 28 000 units of diphtheria antitoxin used in this case seems to us less than half an adequate dose The use of sulfonamides constitutes a valuable adjuvant treatment in diphtheria —F I]

Types of Diphtheria Bacilli in New York City in 1940 are described by Erich Seligmann[5] (Columbia Univ) Among 181 strains isolated from patients and carriers during 1940 5 were found which fermented starch and glycogen and resembled the gravis type The remaining 176 strains failed to ferment these polysaccharides Of these 176 strains, 96 possessed the characteristics of the mitis type while 80 differed in some respect from either group The latter were therefore designated as indeterminate strains Thus an extremely high percentage

(5) Am J Hyg Sect B 34 1 5 13 [illegible] mber 194[illegible]

of all strains eluded more precise definition Eleven (6 1 per cent) strains were avirulent including 10 of the mitis group and 1 of the indeterminates none of the starch fermenters was avirulent No relationship could be established between type of bacilli and clinical severity In areas with rare incidence and mild character of diphtheria such as New York City in 1940 it was not possible to identify the diphtheria bacilli according to the European scheme of type differentiation

Present Status of Immediate Tellurite Test for Diphtheria Howard R Bierman and Richard W Maxwell[6] (Washington Univ) describe results obtained with the immediate tellurite test in 117 patients hospitalized with exudates or diphtheric membranes of the pharynx Twenty nine were shown not to have diphtheria but gave positive reactions to the tellurite test (false positive reactions) In 84 cases the tellurite test was accurate there was a negative reaction in 38 cases with negative cultures and a positive reaction in 46 cases with positive cultures for Corynebacterium diphtheriae

In four cases false negative results were obtained with the test i e no blackening of the membrane with a report of a positive culture for Corynebacterium diphtheriae In one of these cases however the virulence test gave negative results The second false negative reaction was obtained on a membrane which had the gross appearance of a diphtheric membrane a repeat application of the tellurite solution 12 hours later gave a positive reaction The two remaining patients had membranes which failed to reduce the tellurite yet bacteriologic studies showed the presence of a virulent strain of Corynebacterium diphtheriae No ill effects accrued from the procedure

Faulty application of the tellurite solution to the membranes of the throat may explain some of the reported false negative results In the throats of diphtheria patients there is frequently found abundant

(6) J A M A 117 1 551 56 Oct 11 1941

over both sides of the chest but no localized dulness Diagnosis was measles bronchopneumonia and possible laryngeal diphtheria Paraldehyde 2 drachms per rectum, 28,000 units diphtheria antitoxin intramuscularly and oxygen by oropharyngeal intubation were given In addition she received 1 Gm sulfapyridine orally followed by 0 5 Gm every four hours Two hours later general condition was fairly good but stridor was more pronounced and she was still rather restless Luminal 1 gr was given and she was placed in a steam tent and in four hours stridor had diminished and color was still satisfactory The next day she felt much better and was sitting up in bed playing There was still some stridor and chest signs were the same as on admission Temperature was 99 4 F pulse 130 respirations 32

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(5) Am J Hyg S t B 34 1 5 137 N vemb r 1941

nose Snuff was administered to younger children

[We are under the impression that local applications of sul fonamides are of less value than administration systematically through the usual oral dosage —Ed]

Nasal Insufflation of Sulfathiazole Powder for Diphtheria Carriers J Goldman and W H Patterson[8] (Manchester England) describe results obtained in 12 patients from whom virulent bacilli were isolated Duration of the carrier state varied from 10 days to 4 months Eleven of the 12 became negative the average interval from beginning of insufflation treatment until repeated negative swabs were obtained being five days In five swabs examined four months later were negative

A single no 15 De Vilbiss powder insufflator can be used for a group of patients Each patient has an individual nasal piece consisting of a piece of glass tubing 1 in long rounded at one end with 1 in of rubber tubing by which it is attached to the insufflator barrel The nasal piece is boiled each time after use Treatment consists of (1) simple nasal toilet (2) insufflation of powder into each nostril using one squeeze of the bulb for infants under 1 year two for those under 3 and three for those over 3 (3) four treatments given between 8 00 a m and 6 00 p m (4) swabbing never less than 12 hours after an insufflation (5) swabbing on alternate days until three consecutive negative cultures are obtained and then seven days after cessation of treatment Nasal insufflation is performed even when throat cultures alone are positive

(8) B t M J 1 641 M y 3 194

thick tenacious mucus which may cover the membrane so effectively as to prevent the tellurite from making actual contact with the membrane This mucus together with the difficulty of visualizing the pharynx of an acutely ill patient adequately, makes application of the solution difficult Prior to the application, the area of the membrane should be swabbed thoroughly for a culture The area to be tested should be cleansed and dried but should not have been recently treated with hydrogen peroxide tannic acid or methylene blue The mouth should be kept open the tongue depressed and the swab dipped in 2 per cent potassium tellurite solution held in contact with the prepared area for 5 to 10 seconds Removal of the mucus and saliva by suction is helpful

A negative tellurite reaction if it contradicts the clinical impression is not sufficiently reliable to justify withholding antitoxin therapy

Chronic Nasal Diphtheria Carriers Joan M Boissard and R M Fry[7] believe that a persistent nasal infection with Corynebacterium diphtheriae depends on an associated hemolytic streptococcic infection which can be eradicated by nasal insufflation of sulfanilamide Sulfanilamide powder was administered intranasally to 26 children with such a heavy double nasal infection which had persisted for periods of 4 to 23 weeks In 24 the nasal infection was eradicated by the first eight day treatment course in 2 eradication was achieved by a second course Two additional nasal carriers with a double infection of 11 and 5 months duration were treated outside the hospital and cured

The authors describe an easily constructed insufflator for use with the sulfanilamide powder Nasal insufflation was performed twice daily in their cases Children who were old enough to cooperate were given a supply of sulfanilamide powder to use as snuff at frequent intervals during the day especially after blowing the

(7) L t 1 610 614 M y 3 194

of several years by the chronic stage The disease is not self limited and the virus appears capable of lying dormant to smoulder again The chronic stage is usually characterized by one or more of the following symptoms a hypertonic state of general muscular rigidity with masklike face (parkinsonism) sleep disturbance involuntary movements respiratory arrhythmias and tics oculogyric crises obesity polyuria or narcolepsy In children especially mental deterioration in either conduct or intellect or both or simple slowness—hebetude—is a frequent sequel The cerebrospinal fluid is clear, colorless and not under pressure and presents 5 100 small lymphocytes and normal glucose and chloride levels

The relationship of the clinical manifestations to the cerebral sites of involvement indicates the affinity of the virus for certain ganglions mental disorders to lesions of the cortex and centrum ovale parkinsonism to destruction of the substantia nigra respiratory disorders to lesions of the pontile nuclei ocular paralyses to the region of the oculomotor nuclei obesity polyuria and narcolepsy to hypothalamic damage

Poliomyelitis is hesitantly classified as an encephalitide Apart from the bulbopontile lesions in man it is doubtful if a condition of polio encephalitis exists Even in epidemics of poliomyelitis the number of cerebral cases is extremely small and doubtfully authentic

Acute benign lymphocytic meningitis includes a group of nervous disorders not of uniform pathogenesis but of similar symptomatology characterized by sudden onset of signs of meningeal irritation Some are due to mild virus infections Coryza or tonsillitis may precede onset of nervous symptoms Onset of signs of meningeal irritation is usually acute presenting severe headache neck rigidity and generalized aching photophobia vomiting and pyrexia of 100 to 103 F An irritable wakefulness bordering on insomnia is more common than drowsiness coma or delirium Convulsions

ENCEPHALITIS

A Clinical Review of Encephalitis is presented by W G Wyllie[9] (Hosp for Sick Children Great Ormond Street London) Encephalitides may be divided into (1) encephalitis due to virus infection, (2) encephalitis of unproved etiology but characterized pathologically by demyelination of nerve fibers and (3) incidental encephalitis in which the brain lesions are not an essential part of the disease but are similar to those occurring in other parts of the body e g typhus

Virus encephalitides include encephalitis lethargica poliomyelitis acute lymphocytic choriomeningitis mumps encephalitis Japanese encephalitis type B St Louis encephalitis and Australian X disease Clinically differences of predilection of some viruses for certain fields of gray matter give rise to distinctions in symptomatology

Encephalitis lethargica now rare when present in epidemic proportions presents symptoms divisible into acute and chronic stages The acute is sometimes fulminating but more often gradual After brief preliminary nasopharyngitis pains in the back and head and slight fever characteristic symptoms appear of ocular paralyses lethargy and disturbances of sleep rhythm Ocular symptoms and facial paralysis are common The ocular pareses tend to clear up after a few weeks Lethargy sometimes amounting to deep somnolence is more common in the acute stage than an irritable or hyperkinetic state combined with choreiform and myoclonic jactitations affecting one or several muscle groups of the trunk or limbs The usual disturbance of sleep rhythm is somnolence by day and restless wakefulness by night Convulsions are rare except in young children The acute stage lasts one to several weeks and can be followed immediately or after a variable interval

(9) P ct t on r 148 111 116 F b u ry 194

giddiness delirium and drowsiness which may deepen into coma Facial nerve palsy is common ocular palsies seldom occur but trismus is frequently present Cerebral signs are diplegia hemiplegia ataxia aphasia dysarthria dysphagia rigidity tremor or choreiform movements Increased tonus of the trunk and limbs as a state of statuesque rigidity with the legs in extension and the arms flexed or extended associated with a staring coma, is often seen and may last for three to nine weeks without change Myelitic signs are those of a transverse myelitis with sensory disturbances and urinary retention Of common occurrence are the absence of knee and ankle jerks and extensor plantar responses Symptoms endure for one to several weeks Mortality is highest in postmeasles and vaccinal cases

Incidental or acute toxic encephalitis includes those cases in young children of mixed meningo encephalitic and myelitic syndromes complicating some bacterial infection There is no true encephalitis Such incidental encephalitis may complicate measles scarlet fever erysipelas streptococcus pharyngeal and otitic infections and bronchopneumonia Nervous symptoms are of sudden onset and resemble those of purulent meningitis In severe cases signs of cerebral and spinal involvement are hemiplegia monoplegia or diplegia urinary retention and absence of deep reflexes with extensor plantars The spinal fluid is under pressure and clear it may contain a fibrin clot and has normal percentages of chlorides and glucose and a normal cell count or moderate increase of lymphocytes Mortality is variable but recovery is often complete

Diagnosis of Epidemic Encephalitis by Complement Fixation Tests Casals and Palacios previously described how the complement fixation test could be used extensively in the study of virus infections of the central nervous system Antigens having no anticomplementary power can easily be prepared from infected mouse brain tissue and by inactivation of the serums

and cranial nerve palsies are uncommon The tendon reflexes are either exaggerated or diminished, and paraplegia with extensor plantars and retention of urine may occur Symptoms usually last one to three weeks recovery is generally complete The cerebro spinal fluid is under pressure, colorless and sterile even though it may appear purulent The cell count varies from 100 to 3 000 per cc Polymorphonuclear cells may predominate early but are soon replaced by 90 to 100 per cent lymphocytes

Mumps meningo encephalitis is rare but may become manifest about the fourth day of glandular swelling Symptoms include high fever severe headache vomiting, drowsiness facial paralysis deafness and signs of myelitis Nervous symptoms rarely last longer than 10 days but nerve deafness may be permanent

Japanese encephalitis type B St Louis encephalitis and Australian X disease present an indistinct clinical picture manifest as meningeal irritation of acute onset with occasional evidence of cerebral involvement The usual symptoms in the Japanese and St Louis encephalitides are high fever drowsiness nuchal rigidity tremor and muscular rigidity with cranial nerve paralysis occurring but rarely In Australian X disease there occur headache, fever vomiting drowsiness convulsions and spasticity Cranial nerve palsy is likewise rare The cerebrospinal fluid is usually under pressure clear and sterile and presents a few to 100 or 200 lymphocytes In nonfatal cases recovery is usually complete

The myelinoclastic encephalitides are constituted clinically by the cases of acute disseminated encephalo myelitis following vaccination and complicating the exanthems—smallpox measles chicken pox German measles—chiefly in children and young adults Menin geal symptoms which commonly appear four to seven days after the appearnace of the primary rash are of sudden onset They include fever headache vomiting nuchal rigidity convulsions pain in the extremities

patients bled 10 days or less after onset reacted positively with Western equine encephalomyelitis antigen whereas that of 42 of 58 patients bled 11 or more days *after onset reacted positively* *In the latter group were* 32 serums obtained 16 35 days after onset 81 3 per cent were positive

In this epidemic by means of the complement fixation test a diagnosis was obtained earlier than by any other method for this reason and also because of the possibility of making observations on a much greater number of specimens it is believed that the complement fixation reaction is more practical than the neutralization test

[The application of the complement fixation test promises to be of great value in both the diagnosis of encephalitis and the study of the epidemiology of the disease The neutralization or protection tests are extremely time consuming and expensive —*Ed*]

Distribution of Vectors of Equine Encephalomyelitis in Massachusetts Results of a mosquito survey carried out in connection with investigations on equine encephalomyelitis are reported by Roy F Feemster and *Vlado A Getting (Massachusetts Dept of Pub* Health) Over 275 000 specimens contained in almost 50 000 separate collections of adults and larvae were identified Larvae formed 91 4 per cent and adults 8 6 per cent of the total The three principal genera culex anopheles and aedes comprised 77 3 11 9 and 6 6 per cent respectively of the total specimens collected

Of the 21 species of aedes found in Massachusetts *19* were represented among the specimens collected Six of these are known to transmit the Eastern virus of equine encephalomyelitis They formed 76 4 per cent of the specimens of that genus collected in the survey and only 6 4 per cent of the total specimens collected Of the six vectors three are salt marsh mosquitoes—Aedes cantator sollicitans and taeniorhynchus they are found only along the coast usually not more than

( ) Am J P b He lth 31 791 802 A g t 1941

at the proper temperature specific reactions are obtained J Casals[1] (Rockefeller Inst) describes results of large scale application of this test for diagnostic purposes in a severe outbreak of epidemic encephalitis in man

Starting early in August and lasting through the middle of September a serious outbreak of encephalitis occurred in several mountain and north central states and in some Canadian provinces at the same time as an epidemic of poliomyelitis making clinical diagnosis extremely confusing Seventy four serums from Manitoba and nine from Colorado were tested for complement fixing antibodies in an attempt to establish diagnosis Each serum was tested simultaneously against the antigens of Eastern equine encephalomyelitis Western equine encephalomyelitis lymphocytic choriomeningitis and St Louis encephalitis In every instance the reaction with the Eastern equine encephalomyelitis lymphocytic choriomeningitis and St Louis encephalitis was negative whereas the number of serums reacting with Western equine encephalomyelitis was large

Of the 83 serums 44 reacted positively with the Western equine encephalomyelitis antigen and 39 negatively Titers of the positive serums as determined by the highest dilution giving a 2 plus or better reaction were 1 2 in 4 cases 1 4 in 6 cases 1 8 in 7 cases and 1 16 or better in 27 cases

The proportion of serums 53 per cent reacting with Western equine encephalomyelitis antigen was high yet perhaps not sufficient in itself to give more than presumptive evidence as to the etiology of the infection But two observations render diagnosis almost certain (1) the proportion of positive serums in connection with the time elapsed since onset of the d e and (2) the results obtained with serums from pa ts from whom two samples of blood have been ob d at different periods after onset Thus the serums only 2 of 25

(1) Am J P b H lth 31 1 81 1 84 De 1941

and boric acid solution Four days later headache of increasing severity developed and examination the next day revealed coated tongue injected throat temperature 100 4 F and pulse 85 He was hospitalized the fourth day of illness with marked nuchal rigidity bilateral positive Kernig sign (more marked on the left) and absence of abdominal reflexes Spinal fluid was slightly cloudy and contained 600 cell Bacteriologic study was negative Anti encephalomyelitis immune horse serum 550 cc intravenously and 50 cc intrathecally was given and 30 gr sulfanilamide followed by 15 gr every four hours Sulfanilamide was discontinued after 36 hours because of lack of benefit The next day there were deep coma with increased nuchal rigidity definite ankle clonus variable knee jerks coarse tremors of the face and extremities and cyanosis of lips and nails Temperature was 104 2 F pulse 130 and respirations 40 Immune serum was again given intravenously and intrathecally The following day symptoms were heightened and intravenous serum was again given

The seventh day of illness there was definite improvement with decreased nuchal rigidity and normal tone of the upper extremities Fifty cc immune serum was given intramuscularly The next two days he showed steady mental and neurologic improvement (eighth and ninth days of illness) There was no essential change until the fourteenth day of illness when he seemed listless and emotionally upset The fifteenth day appearance and mental reactions were decidedly worse There was marked tremor of the lids tongue and muscles around the mouth He was listless had a vacant stare and complained of frontal headache Neurologic signs showed improvement except for marked tremor of the head Spinal fluid was clear except for a few flecks on stirring Serum sickness was present at this time The sixteenth day the patient had difficulty in swallowing and breathing The picture was that of severe parkinsonism with mutism Amphetamine (benzedrine) sulfate histaminase and vitamin B complex were given Recovery was gradual and 43 days after onset of the original illness the patient was essentially normal

[This interesting case report is of great value because it contradicts the common idea that serums are of no value in virus infections because of the intracellular invasion of the virus —Ed]

5 miles from the nearest salt water The remaining three are fresh water species—Aedes atropalpus triseriatus and vexans the first occurs mainly in the Connecticut River Valley and the other two are found throughout the state Three of the vectors—Aedes vexans cantator and sollicitans—comprised respectively 25 1 22 5 and 20 4 per cent of the total aedes collected The other three comprised only 8 4 per cent

The peak of the prevalence of the vectors was reached late in August They were therefore most prevalent just before the date of the peak of the 1938 outbreak of equine encephalomyelitis

Vectors of equine encephalomyelitis seldom enter buildings Over 60 per cent of the mosquitoes caught on man were vectors but less than 6 per cent of those captured inside houses were in this group indicating that the danger of bites by vectors is perhaps 10 times greater outdoors than indoors

Aedes vexans was probably the most important vector of equine encephalomyelitis in Massachusetts in 1938 This species is 5 15 times as numerous as Aedes triseriatus the only other known vector found in all areas where the disease was prevalent that year Aedes vexans is an ubiquitous breeder and difficult to control especially in rural areas

In Massachusetts salt marsh mosquitoes have been greatly reduced in the last 10 years by active control measures It is likely that equine encephalomyelitis might have been more prevalent along the coast if the salt marsh vectors had been as numerous as in earlier years

Equine Encephalomyelitis in a Laboratory Technician with Recovery Herman Gold and Bettylee Hampil[3] (Glenolden Pa) report a case

Man 29 accidentally splashed the contents of a virus-inoculated egg on his face close to the right eye The face was cleansed and the eye irrigated with mild silver protein

(3) A h Int Med 16 5 6 69 M 1 194

INFECTIOUS JAUNDICE (WEIL'S DISEASE)

Study of Certain Epidemiologic Features of Leptospiral Jaundice in Baltimore is presented by Thomas C Ward and Thomas B Turner[5] (Johns Hopkins Univ) A summary of the incidence positive agglutination tests for Leptospira icterohaemorrhagiae among selected groups is shown in the table The highest incidence was noted among poultry dressers meat packers likewise showed a higher incidence than might be expected in the general population Rats infested all such establishments surveyed and rats taken from one were shown to be carriers of virulent leptospira Infected rats elim

DATA ON SELECTED GROUPS OF PERSONS FOR AGGLUTININS TO LEPTOSPIRA ICTEROHAEMORRHAGIAE

G o T D	P rsons Te	Pos tive Aggluti tion T s	
		N	%
Poultry dressers	75	13	17 3
Meat packers	48	3	6 3
Candy makers	24	0	0
University students	146	0	0
Hospital patients	234	21	9 0
Specimens from Wassermann laboratory	294	9	3 0
Jaundice cases—Pennsylvania	10	0	0
Total	830†	45†	5 4

I l d s pat t wh is ls l d d g p f po lt y d rs
† Does t l d dupl t

inate leptospira in the urine In these establishments the employes worked in a damp environment often in direct contact with stagnant water which is subject to pollution with rat urine

The premises of the candy making establishment which was surveyed were on about the same sanitary

(5) Am J Hyg 35 1 133 J ry 194

Swine Erysipelas and Erysipeloid are discussed by W L Boyd[4] (St Paul Minn) Swine erysipelas is an acute or chronic infectious disease caused by the erysipelas bacillus (Erysipelothrix rhusiopathiae) It is manifested by dermatitis gastro enteritis hemorrhagic nephritis swelling of the spleen and degeneration of the heart liver and muscles It occurs chiefly in swine, but man sheep pigeons turkeys mice and rabbits are susceptible

Erysipeloid is a disease of man caused by an organism of the genus Erysipelothrix and is known in medical circles as the erysipeloid of Rosenbach In recent years it has been reported as occurring among fish handlers abattoir employes rendering plant workers and students and practitioners of veterinary medicine Duration of the disease is usually three weeks Rest and heat are essential in treatment The affected extremity should be carried in a sling or preferably, in a splint Locally constant wet dressings with 12 per cent ichthammol in alcohol are advocated Roentgen therapy is of uncertain value Recently it has been determined that in the cutaneous form of the disease in man local application of immune serum packs is especially valuable

(4) J u IL nc t 6 11 13 June 1942

with or without chill and later jaundice with muscular pains gastro intestinal disturbances conjunctivitis albuminuria and epistaxes should suggest Weil s disease Jaundice occurring during an acute illness associated with hepatomegaly but without splenomegaly or general adenopathy should also be suggestive Furthermore in any case of serous meningitis this disease should be carefully considered

Weil s disease may vary from an extremely mild illness without jaundice and resembling influenza to a very severe prostrating illness with fatal outcome Abrupt onset leukocytosis and albuminuria differentiate it from catarrhal jaundice Nephritis occurs in 89 per cent of cases with jaundice and in 75 per cent without jaundice Diagnosis of the disease without jaundice is extremely difficult Noteworthy is the outstanding apathy of the patients

Prognosis is influenced by age presence or absence of jaundice cardiac function and presence or absence of uremia With increasing age prognosis becomes proportionately graver The fatality rate among patients without jaundice is negligible Among those with jaundice the fatality rate for all ages is 16 32 per cent Prognosis is unfavorably influenced by uremia particularly if oliguria or anuria exists Increased urinary output with fall in nonprotein nitrogen are favorable signs although death may still occur from cholemia or cardiovascular collapse

Active immunity may be produced by injection of killed organisms Inada *et al* used immunized horse and convalescent human serum and reduced mortality from 30 6 to 17 3 per cent While it has not been conclusively demonstrated that serum exerts any specific action on the pathogenic organisms it seemingly has a beneficial effect when administered within four days of onset of the disease It is probable that a high carbohydrate low fat diet would prove useful in treatment of those patients with jaundice

level as the others and rats were numerous yet the employes worked in a dry environment This may have accounted for the absence of evidence of lepto spiral infection in the group tested In contrast to the first three groups, the student group comprised per sons who as a rule do not come into close contact with wild rats particularly under circumstances in which water might serve as a vehicle of transmission

The hospital group among which there were 8 per sons with acute Weil s disease and 13 other persons with evidence of past infection is not representative of either the general population or of a particular occupa tional group The serums were collected from patients with symptoms slightly suggestive of leptospiral infec tion and not from a random sample of all hospital pa tients The serums taken from specimens submitted for routine tests for syphilis properly were not a part of this survey and were tested originally for another pur pose While they represent in general an adult dis pensary population it cannot be said with certainty that they represent a random sample of that group

The authors also report that virulent Leptospira icter ohaemorrhagiae were demonstrated over a two month period in a well used as a source of drinking water Three cases of Weil s disease were traced to this well as the probable source of infection

Weil s Disease Howard K Rathbun and Julius M Waghelstein[6] (Baltimore City Hosps) report six cases occurring within 20 months Diagnosis of Weil s dis ease would probably be made more frequently if it were considered more often in the differential diagnosis of jaundice of unknown etiology or of any obscure illness characterized by muscle pains conjunctivitis and fever of rather sudden onset Final diagnosis rests on ag glutination reactions and guinea pig inoculations with blood and urine History of contact with the urine of wild rats is valuable Sudden onset of a febrile illness

(6) Ann Int M d 15 395 407 S pt mber 1941

INFLUENZA

Antibody Response of Human Beings Following Vaccination with Influenza Viruses G K Hirst E R Rickard Loring Whitman and F L Horsfall Jr (Rockefeller Found) used 11 different preparations of influenza virus to vaccinate large groups of human beings Antibody response was measured by means of the in vitro agglutination inhibition test and the geometric mean titers of serums taken two weeks after vaccination were compared

There was a wide individual variation in antibody response to the same preparation of influenza virus administered subcutaneously The amount of antibody produced by a group with a low prevaccination antibody level was nearly the same as that produced by groups having higher initial levels Use of the X strain of distemper virus in preparation of an influenza vaccine did not enhance the antigenicity of the influenza virus present Within certain limits the mean antibody response increased as the amount of virus injected was increased When large amounts of influenza A virus were given the antibody response was of the same order of magnitude as that which occurred following actual infection by this virus

When the vaccine was prepared from allantoic fluid there was no significant difference in antibody response of human beings given active virus formalin inactivated virus heat inactivated virus and virus inactivated by the drying process Ground infected chick embryos when diluted with infected allantoic fluid caused greater antibody response than allantoic fluid alone (when the virus remained active) Antigenicity of such a preparation was diminished when the virus was inactivated by formalin

Antibody levels six and nine weeks after vaccination

(8) J Exp Med 5 495 511 May 1942

Positive Agglutination Tests in Suspected Cases of Weil s Disease Using the microscopic agglutination test Ardzroony Packchanian[7] (Nat l Inst of Health) found agglutinins for type I Leptospira icterohaemor rhagiae in the serums of 40 persons suspected of having Weil s disease during the past four years These cases were distributed as follows Connecticut 1 Louisiana 4 Maryland 9 Massachusetts 2 Michigan 2 Mis souri 2 Nevada 1 New Jersey 2 New York 5 Ohio, 4 Pennsylvania 1 Virginia 4 West Virginia 2 and District of Columbia 1 Thirty six cases occurred in adult males one in an adult female and three in chil dren Occupation or place of residence in most instances was such that contact with wild rats might be expected Eight of the 40 patients were Negroes the others were white Six of the 40 cases terminated fatally

With the freshly prepared formalinized antigen of type I Leptospira icterohaemorrhagiae the agglutina tion titer in 5 cases ranged from 1 300 to 1 1 000 and in 8 from 1 3 000 to 1 10 000 in each of the remaining 27 cases it was about 1 30 000 or higher Agglutination reactions in these dilutions were prompt and completed within two hours

Sixty one blood samples from 36 persons with Weil s disease after refrigeration storage at 5 C for 169 to 1 078 days were retested and with four exceptions were found to give strong agglutination reactions with type I Leptospira icterohaemorrhagiae The agglutina tion titers of this group approached or were identical with the original agglutination titers

Blood samples from 20 jaundiced dogs likewise gave strong agglutination reactions with this organism in dilutions of 1 30 000 and higher Also noted was the isolation of virulent strains of Leptospira icterohaemor rhagiae from wild rats (Rattus norvegicus) captured in Detroit New York City and Washington D C

(7) Pub Hlth Rep 56 14 2156 [illegible] 1941

lectively it was found that influenza A had occurred in about 6 per cent of the controls and about 3 per cent of the vaccinated individuals of these institutions This indicates a decrease of approximately 50 per cent in the incidence of the disease among the vaccinated groups

Results of Active Immunization against Epidemic Influenza from 1937 to 1940 Morris Siegel Ralph S Muckenfuss Morris Schaeffer Harriet Leslie Wilcox and Ann G Leider[1] (Dept of Health New York City) report results of a study of epidemic influenza and the effects of inoculation of active influenza A virus at Letchworth Village N Y Serologic response to the inoculations and to acute infections of the upper respiratory tract was observed from 1937 to 1940 by complement fixation and neutralization tests

The average antibody titer of the inmate population declined considerably within four months after the 1937 epidemic It remained at a low level for 20 months until February 1939 when there was a significant increase in antibodies attributable to infection during the 1939 influenza A epidemic The elevated titer fell to low preepidemic levels within several months and remained so throughout 1940 when there was no influenza A epidemic Among virus vaccinated individuals an increase in antibodies for a short period was observed each year following annual inoculation of influenza virus In nonepidemic years of influenza A the elevated titer following inoculation declined to preinoculation levels within a few months During the 1939 influenza epidemic there was a secondary rise among those infected while the postinoculation titer was falling and there was a prolonged rise among those infected before the postinoculation titer had reached its peak

During nonepidemic years of influenza A there was no significant increase in the average antibody titer of the population following acute infection of the upper res-

(1) Am J Hyg 35 55 96 J ry 194

showed a marked drop from the two week postvaccination levels In a small group the antibody levels at five months were still further reduced Individuals with higher titers tended to lose their antibodies faster than did those with lower titers

Influenza Results of immunization of human beings against influenza A with vaccine prepared from chick embryos inoculated with both influenza A virus and the X strain of canine distemper virus are described by Frank L Horsfall Jr[9] (Rockefeller Found) Large groups of persons in various institutions were given a single subcutaneous injection of the complex vaccine during the fall of 1940 Somewhat larger groups in the same institutions were left as unvaccinated controls Four months later outbreaks of influenza occurred in a number of these institutions Because it had been found that the etiology of influenza was diverse and since the vaccine was directed only against influenza A it was considered essential to determine by laboratory tests the etiology of as many cases as possible in both control and vaccinated groups to assess accurately the possible efficacy of the vaccine as a prophylactic agent against influenza A

There were wide differences in the proportion of cases of influenza in the control groups which showed evidence of having been infected by influenza A virus in various institutions For example in one institution only 53 per cent of the clinical cases were of this variety, while in another 92 per cent of cases were caused by this virus Although lots of vaccine of approximately equal antigenic potency were used in each of these institutions there was considerable variation in the results In one institution there was no difference between the incidence of influenza A in the control and the vaccinated groups In all the other institutions however the incidence was somewhat lower among vaccinated persons than among controls Considered col

(9) Ann I t M d 15 811 816 N mbe 1941

Specimens of serge sheet dust and glass slides were impregnated and the viable virus extracted before and after drying Between 1 and 10 per cent of virus withstood drying on the serge and dust and 10 per cent or more on the glass slides When squares of sheet were impregnated with 0 7 cc virus suspension an amount sufficient to saturate the square almost completely 1 per cent of virus survived drying but when 0 1 cc suspension was applied as a drop in the center there was survival of little more than 0 01 per cent A similar difference in survival depending on the degree of impregnation did not occur with the serge the reason for which is not apparent

The time the dried virus remained alive was estimated There was little depreciation after three days 10 per cent might persist for a week and 1 per cent for two weeks Disappearance of virus was much more rapid when impregnated materials were kept at 37 C or in the light The largest amount of dried virus was obtained on glass slides

[This valuable report aids in the understanding of the ease of transmission of influenza —Ed]

Effects of Certain Detergents on Influenza Virus (Types A and B) Albert P Krueger[3] (M C U S N P) tested representative detergents for the capacity to inactivate influenza viruses types A and B The detergents included (1) zephiran (2) tergitol penetrant no 7 (3) an alkaline cleansing agent containing tri sodium phosphate (oakite no 63) (4) general purpose soap solution (Ivory soap cake)

Despite its well established bactericidal properties for organisms such as Staphylococcus aureus and Escherichia typhi zephiran failed to inactivate the test virus preparations even after one hour of exposure to a concentration of 1 10 000 Tergitol penetrant no 7 in concentrations as high as 1 2 000 did not destroy the viruses in dense lung suspensions With dilute virus

(3) U S N M Bull 40 6 6 1 J 1 194

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(3) U S N M B U 40 6 631 J l 194

preparations there was measurable inactivation after one hour A 1 per cent solution of oakite no 63 was ineffective against concentrated type A virus although the pH of the mixture was well beyond the viruses' stability range The activity of type B virus mixed with 1 per cent oakite no 63 was definitely reduced A 1 per cent soap solution rendered dense lung suspensions of type B virus noninfectious within 40 minutes but only partially destroyed the corresponding type A virus preparation Dilute viruses of both types were entirely lacking in infectiousness after being in contact with 1 per cent of 0 1 per cent soap solution for 15 minutes Lower concentrations of soap displayed only partial and irregular inactivating capacity

[It is comforting to know that fairly dilute soap solutions are effective germicides for influenza virus —Ed]

Treatment of Influenzal Meningitis with Sulfadiazine Wallace Sako Chester A Stewart and Joel Fleet[4] (Charity Hosp New Orleans) report the sulfadiazine *treatment of seven children with influenzal meningitis* Five were discharged as cured and have remained well Three of these recoveries occurred with drug therapy alone while the other two patients received both anti serum and the drug Two fatalities occurred in young infants one following cisternal puncture and the other after a prolonged course complicated by severe infected burns chickenpox and bilateral mastoiditis with left lateral sinus thrombosis

Clinical response to sulfadiazine was dramatic and prompt in all cases in which recovery occurred Stupor and coma disappeared in 36 to 48 hours and spinal fluid cultures became sterile in an average of 5 days after institution of drug therapy Unfortunately sulfa diazine levels in the blood and spinal fluid were not followed closely in this series It is significant however that the blood concentration of the free drug under maximum dosage was always above 10 mg per cent and

(4) J A M A 119 3 331 May 3 194

was sometimes as high as 25 mg per cent with an average of 20 mg per cent Spinal fluid concentration of sulfadiazine when determined ranged from 9 7 to 15 mg per cent Therapeutic success in this series is ascribed to the relatively high cerebrospinal fluid levels of sulfadiazine that were obtained An illustrative case terminating in recovery is presented

Girl 3 weighing 37 lb had been well except for a slight head cold for one week prior to admission On the day of admission she had a chill followed by fever Drowsiness and stupor ensued Examination revealed a stuporous child lying quietly in bed with both legs flexed Rectal temperature was 10? 6 F pulse 120 and respiration 35 A slight nasal discharge and mild redness of the posterior pharynx were present The neck was rigid and Kernig s and Brudzinski s signs were positive The lungs presented dulness to percussion with increased breath sounds and crepitant rales in the right upper lobe Deep reflexes were slightly increased

Spinal tap revealed cloudy fluid Globulin was increased chlorides were 750 mg and sugar was 30 mg per cent The cell count was 12 000 95 per cent of which were polymorphonuclear cells Gram negative pleomorphic bacilli were seen on smear which on culture proved to be Haemophilus influenzae The blood was likewi e positive for the influenzal bacillus The erythrocyte count was 3 950 000 hemoglobin 55 per cent (Sahli) and leukocyte count 15 000 with 90 per cent polymorphonuclear cells The urine was normal

An initial dose of 30 gr sulfadiazine was given by stomach tube followed by a maintenance do e of 2 gr per lb body weight daily divided into six equal do es and administered every four hours This dose was continued for nine days at which time it was reduced to 1½ gr per lb body weight daily until the drug was discontinued 19 days after it was started A total of 80 Gm sulfadiazine was given

Stupor deepened into coma the day after admission The following day the patient was itting up in bed eating and f eling much better Three days after admission she was afebrile Seven days after in titution of sulfadiazine therapy the spinal fluid was clear and culture was negative At this time the sulfadiazine level in the spinal fluid was 11 mg per cent of free sulfadiazine while the blood level was 17 mg per cent Only two spinal punctures were done Small blood transfusions were also given The patient was discharged 23 days after admission presenting no evidence of residual cere

preparations there was measurable inactivation after one hour A 1 per cent solution of oakite no 63 was ineffective against concentrated type A virus although the pH of the mixture was well beyond the viruses stability range The activity of type B virus mixed with 1 per cent oakite no 63 was definitely reduced A 1 per cent soap solution rendered dense lung suspensions of type B virus noninfectious within 40 minutes but only partially destroyed the corresponding type A virus preparation Dilute viruses of both types were entirely lacking in infectiousness after being in contact with 1 per cent of 0 1 per cent soap solution for 15 minutes Lower concentrations of soap displayed only partial and irregular inactivating capacity

[It is comforting to know that fairly dilute soap solutions are effective germicides for influenza virus —Ed]

Treatment of Influenzal Meningitis with Sulfadiazine Wallace Sako Chester A Stewart and Joel Fleet[4] (Charity Hosp New Orleans) report the sulfadiazine treatment of seven children with influenzal meningitis Five were discharged as cured and have remained well Three of these recoveries occurred with drug therapy alone while the other two patients received both anti serum and the drug Two fatalities occurred in young infants one following cisternal puncture and the other after a prolonged course complicated by severe infected burns chickenpox and bilateral mastoiditis with left lateral sinus thrombosis

Clinical response to sulfadiazine was dramatic and prompt in all cases in which recovery occurred Stupor and coma disappeared in 36 to 48 hours and spinal fluid cultures became sterile in an average of 5 days after institution of drug therapy Unfortunately sulfa diazine levels in the blood and spinal fluid were not followed closely in this series It is significant however that the blood concentration of the free drug under maximum dosage was always above 10 mg per cent and

(4) J A M A 119 3 331 My 3 1942

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bral damage, and she remained afebrile throughout the following five week period during which the case was followed up

Because of its easy absorption low toxicity ready secretion into the cerebrospinal fluid relative small degree of acetylation slow excretion its property of remaining in the blood stream in high concentration and its superior bacteriostatic properties against the common pyogenic organisms sulfadiazine is seemingly the drug of choice in purulent meningitis Spinal punctures and drainage were done infrequently in this series because of the prompt clinical improvement of all patients who recovered This suggests that influenzal meningitis can be treated successfully without resort to frequent spinal punctures when sulfadiazine is given liberally It is tentatively suggested that during the acute stage of influenzal meningitis large doses of the drug should be administered so that blood levels are always above 10 mg per cent of the free drug preferably 15 20 mg per cent and that the spinal fluid drug level is maintained around 10 mg per cent or higher After apparent cure it is suggested that the patient be maintained on reduced doses of the drug for at least two additional weeks

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MALARIA

Treatment of Malaria, in the opinion of Wendell S Dove[5] (Barranquilla Colombia) should be determined solely by the symptomatic indication presented and the urgency of symptoms rather than the type of malaria Successful treatment is based on judicious use of the several specific drugs Every patient should have the following minimal treatment taking approximately four weeks Doses given are for average adults weighing 150 lb or more

1 First period atabrine $1\frac{1}{2}$ gr thrice daily during the febrile period and for four days thereafter

(5) Am J Trop Med 24 May 194

2 Second period quinine (sulfate or other soluble salt) 5 gr four times daily for seven days
3 Third period atabrine 1½ gr thrice daily for five days
4 Fourth period quinine 5 gr thrice daily for five days
5 Fifth period quinine 5 gr plasmochin 1/6 gr thrice daily for five days

Modifications of this regime are described In chronic frequently relapsing or recurring cases the minimum treatment is followed by a 10 day rest period where upon the third fourth and fifth periods of treatment are repeated in numerical order If atabrine causes toxicity longer intervals must be allowed between its adminis tration using 15 gr quinine daily while waiting Any partially treated latent or chronic case can be held in abeyance with this amount of quinine In neglected cases with many gametocytes plasmochin should be given during the second period of treatment using 1/6 gr three times daily in conjunction with the quinine

Dove believes that there are no indications for paren teral use of quinine or for intravenous use of atabrine However atabrine 4½ gr in 7 5 cc water may be given intramuscularly if oral medication is not possible if the temperature exceeds 104 F if the infection is concen trated in an important organ or system or if overwhelm ing infection exists Such dosage may be repeated every 12 hours

Nursing Care of Malaria is described by Nell E Mills (Charity Hosp New Orleans) With onset of the chill in the malarial patient a warm blanket well tucked in is placed around the patient One hot water bottle is applied at the feet another at the small of the back care being exercised to place them between blanket and sheet and not directly next to the patient Warm drinks such as hot lemonade with a small amount of whisky or hot tea or coffee are given There is less danger of nausea if the liquid given is light and free of fats

With abatement of the chill the patient begins to feel warm and then too warm Temperature readings at this time reveal a rise to about 104 F Too sudden chilling now can produce another chill with an even higher temperature rise Measures to reduce temperature are gradually instituted An ice bag is placed at the patient s head he is given cool but not iced liquids to drink all that he can tolerate Finally an alcohol sponge to the entire body is given Nausea and vomiting should be prevented if possible to avoid dehydration Unsweetened fruit juices and water are the best fluids to administer They should be forced if tolerated well but not if they cannot be retained An antipyretic is usually given to relieve headache as well as fever

With reduction of temperature profuse perspiration appears Efforts to keep the patient dry are at first fruitless but perspiration shortly abates whereupon a complete or partial bed bath with change of linen is indicated to insure restful sleep

Varying Infectiousness of Different Patients Infected with Vivax Malaria Mark F Boyd[6] (Tallahassee Fla) states that patients infected with Plasmodium vivax exhibit wide variations in their infectiousness for *Anopheles quadrimaculatus* *Based on the infection resulting in anophelines* patients have been distinguished as good and poor infectors These have not in general differed markedly in gametocyte densities except that higher densities were seldom observed in the poor infectors The qualitative and quantitative infection of the mosquitoes infected on patients of either category varies directly with gametocyte density although at any given density the qualitative infection arising from a feed on a poor infector will probably be lower than that resulting from an application to a good infector of comparable density

Although *gametocyte densities in good infectors* tend to be slightly higher than in poor infectors the

(6) Am J Tr p Med 3 81 J ary 194

most striking difference lies in the parity of the sexes in the good infectors and deficiency of males in the poor ' infectors However gametocyte density is not a reliable guide to the probable resulting qualitative infection of mosquitoes although Boyd s data establish these relationships

Varying proportions of susceptible and refractory mosquitoes in different lots may affect the qualitative infection *of any lot particularly when gametocyte density* is low Also the gametocytes of poor infectors may be inferior perhaps in vitality to those produced in good infectors

Role of Parasite Pigment in the Malaria Paroxysm Dempsie B Morrison and W A D Anderson[7] (Univ of Tennessee) record differences between the symptoms of ferrihemate intoxication and malaria infection in the monkey Ferrihemate injected monkeys die in shock with symptoms suggesting capillary blocking in vital organs or recover rapidly and completely after a brief acute toxic reaction However ferrihemate is not a causative agent in the malaria paroxysm of monkeys because the pigment is not liberated in soluble form from *the* parasite

Report on a Group of Cases of Benign Tertian Malaria Which in Early Stages Simulated German Measles C M Vaillant[8] reports on a group of about 50 men from one unit who presented a rash indistinguishable from that of German measles Conjunctival injection was present with retro-ocular pain and frontal head ache Temperatures ranged from 101 to 103 F No patient *presented occipital adenitis which is usually pres* ent in German measles The spleen was palpable in at least seven cases

Symptomatic treatment being of no avail blood films from all patients were examined and the parasite of benign tertian malaria was found in each instance Qui

(7) P b H lth R p 7 161 174 J n 30 194
(8) J R y A my M C p 77 59 60 N emb 1941

nine treatment led to complete recovery with disappearance of the rash The opinion of consultants was that the morbilliform rash was due to prickly heat arising from excessive sweating in the malarial paroxysms A history of definite exposure of the unit for one night near a swamp was obtained and the date of this exposure correlated with the onset of symptoms was consistent with the incubation period of benign tertian malaria

Are the Experimental Data of Therapeutic Malaria Applicable to Conditions Obtaining in Nature? Ch W F Winckel[9] (Amsterdam) states that as a rule experience with induced malaria in paretics may be applied to ordinary malarial patients provided the following points are kept in mind (1) If paretics are infected by mosquito bite their reaction to drugs differs from that in ordinary patients only in that the bodily resistance incited by a considerable number of fever attacks promotes the action of the drugs as a consequence somewhat smaller doses suffice and clinical relapses are fewer (2) In treating paretics whose malaria has been induced by blood inoculation the possibility of relapses in benign tertian and quartan malaria may be ruled out altogether Here again smaller doses than used in ordinary practice suffice

Inoculation of Canaries with Sporozoites from Isolated Malarial Oocysts It has been demonstrated that artificially inoculated salivary gland sporozoites of avian malaria are infective to the vertebrate host but the question of the infectivity of sporozoites obtained from the stomach oocysts and the body cavity is not definitely settled M M Brooke[1] (Johns Hopkins Univ) reports experiments wherein seven stomach oocysts were inoculated into clean canaries six being inoculated intravenously and one subcutaneously No infections arose in the canaries as determined by blood examination subinoculation and reinoculation These negative

(9) Am J Trop Med 1 89 794 Novembe 1941
(1) Am J Hyg 35 134 137 Ja uary 194

results tend to indicate that the sporozoites prior to leaving the oocysts are not infective to the vertebrate host when artificially inoculated It is possible that the inoculums used contained an insufficient number of sporozoites to produce infection or that the sporozoites were not sufficiently matured

Anopheles Pseudopunctipennis (Theobald) a Vector of Malaria in Mexico The conclusion of Hoffmann that Anopheles pseudopunctipennis is a vector of malaria is confirmed by observations made by Luis *Vargas Guillermo Casis S (Dept of Pub Health Mexico)* and Walter C Earle (Champaign Ill) in Temixco Morelos Mexico where the malaria incidence is high in a rice growing region and Anopheles pseudo punctipennis the only mosquito of any importance It reached a high density entered homes readily showed a relatively high preference for human blood could be infected experimentally and was found infected in Nature Further studies are indicated however before concluding that it is an important vector in all the higher plateaus where it is found with a much higher proportion of Anopheles aztecus or in the coastal re gions where it is found with Anopheles albimanus and apparently not often in as high a density as in the region reported on here

Comparative Susceptibility of Two Strains of Anoph eles Quadrimaculatus to Infection with Human Malaria Parasites is described by Mark F Boyd[3] (Station for Malaria Research Tallahassee Fla) The quadrimacu latus strains concerned were one from Tallahassee and one from Wilson Dam Ala (T V A) Observations in dicate a close parallelism in the susceptibility of these *two insectary strains of Anopheles quadrimaculatus to* both Plasmodium falciparum and Plasmodium vivax

Malaria Reconnaissance of the Province of Camaguey in Cuba is reported by Henry P Carr Joaquín Fernan

(2) Am J Trop Med 1 7 9 783 Nov 1941
(3) Ibid 7 1 53

dez Melendez and Aristides Fernandez Melendez[4] Camaguey Province is characterized by certain areas of moderate endemicity and areas of negligible to light endemicity. The occurrence of the areas of moderate endemicity seems to follow a pattern related to certain factors of topographic and natural drainage. The areas of moderate endemicity are situated in the western two thirds of the North Camaguey coastal plain and the central division of the Great Camaguey Plain. Municipalities with the highest spleen indexes are Esmeralda, Moron, Camaguey, Guaimaro and Florida. It is likely that at times the endemic conditions encountered in the survey will be superseded by more or less extensive and severe epidemics when local conditions are most favorable for production of the anophelines which are the vectors of the disease and when other factors also may be favorable. Anopheles albimanus is the most important vector of malaria in Camaguey Province.

MEASLES

Inefficiency of Immune Globulin in Prophylaxis of Measles during Adolescence. J. Roswell Gallagher[5] (Phillips Acad., Andover, Mass.) gave 8 cc. immune globulin (measles antibody) to 84 boys aged 13-18 in an attempt to prevent measles. Thirty eight boys of similar age range were controls. Forty per cent of the treated group developed measles in 28 days and 52 per cent of the controls developed measles in the same period. Of the 69 students inoculated more than 10 days before the rash appeared, 19 (27 per cent) developed measles, 5 of these cases being modified. Gallagher concludes that a dose of 8 cc. immune globulin given early in the incubation period is not efficient in preventing or modifying measles in this age group.

(4) Am. J. Trop. Med. 1: 39-750, November, 1941.
(5) Am. J. M. Sc. 203: 880-882, June, 194

MENINGITIS

Lumbar Puncture as Factor in Pathogenesis of Meningitis On the basis of a survey of 207 cases of pneumococcic meningitis in infants and children Laurence G Pray[6] (Columbia Univ) concludes that lumbar puncture is not a factor in production of meningitis Pneumococcic meningitis is rarely encountered except when a pneumococcic infection has already been established in some part of the body In the series reviewed infection or trauma about the head was found to be the salient factor in the production of meningitis with pneumonia next in frequency Blood culture positive for pneumococci was obtained in 53 per cent of cases In 13 cases lumbar puncture was performed before onset of meningitis Approximately 80 per cent of the 207 patients were under 2 the age period when resistance to infection is lowest The greater susceptibility of patients in this age group to pneumococcic meningitis was further shown by analysis of 416 cases of pneumococcemia In this series meningitis developed in approximately 30 per cent of patients under 2 and in approximately 10 per cent of those over 2 whether or not lumbar puncture was done These data are in contrast to conclusive experimental evidence that lumbar puncture makes the meninges more susceptible to infection as demonstrated by the production of meningitis in the presence of bacteremia While some danger may exist it must nevertheless be faced because diagnosis of meningitis is frequently impossible on the basis of symptoms and physical signs alone and with the new chemotherapeutic agents now available the prognosis may be affected by the ability to make an early diagnosis

[This is an exceedingly valuable study because use of lumbar puncture for early diagnosis leads to early treatment with a maximum chance for good therapeut esults The not on that it is dangerous leads to hesitat on with results often prejudic al to complete recovery —Ed]

(6) Am J D Ch ld 6 95 308 A u t 1941

Meningitis Due to Salmonella London is described in a case reported by K F Wilsdon and Anne Gibson[7]

Man 61, complained of leg pains, vomiting, restlessness and urinary retention beginning the day before admission Night sweats had occurred four days previously Spastic paralysis of the legs had existed for 20 years On examination the patient was comatose and exhibited spasmodic movements of the extremities Temperature was 101 F and pulse rate 92 The pupils reacted to light and in accommodation There was right supranuclear facial paresis Urine was withdrawn by catheter

Lumbar puncture revealed turbid yellow spinal fluid under normal pressure Cerebrospinal fluid revealed white cells, 4 500 per cu mm polymorphonuclear leukocytes 89 per cent, lymphocytes 9 per cent, endothelial cells, 2 per cent red cells 2 plus short gram negative bacilli in films total protein, 2,200 mg per cent globulin (Pandy's test) positive sugar decreased Wassermann reaction, negative Cultures of the cerebrospinal fluid revealed an organism of the salmonella group identified as the London type This organism was agglutinated by the patient's serum in 1 320 dilution

Treatment was begun with 2 Gm M & B 693 soluble intramuscularly every four hours The seventh day the patient was able to take sulfapyridine orally and was more responsive The twelfth day hypostatic pneumonia was detected and he died the sixteenth day of illness

The salmonella organism had been isolated from three later specimens of cerebrospinal fluid as well as post mortem from the gallbladder ileum and meninges but not from the colon spleen liver or heart blood Autopsy revealed chronic purulent meningitis mainly over the anterior half of the vertex

Since the organism concerned in this case was grown from the gallbladder and ileum which also showed histologic evidence of inflammation it seems probable that the meningitis was a blood borne infection from the alimentary tract

(7) Lancet 1 66 666 May 4 1941

PLAGUE

The Known and Unknown in Plague K F Meyer[8] (Univ of California) states that investigations of epizootic and enzootic plague areas in the western part of the United States have established the existence of spontaneous infections or reservoirs in 31 rodents and rabbits The persistence of sylvatic plague reservoirs was first suspected following periodic rodent epizootics which arise from plague bacilli biologically identical with the organisms isolated from rats or from wild rodents on the American or other continents As a whole the host relationship on the North American Continent does not differ from that proved for South east Russia Transbaikalia South Africa and other sylvatic plague regions where the infection remains localized since a particular fauna maintains the infec tive agent The flea is the indispensable vector in proga gation of plague among wild rodents

A survey of case histories shows that hunting trap ping skinning of sick or burying of dead squirrels and their predators the tilling of fields or temporary or extended sojourn of human beings in enzootic plague areas is connected with a certain but definitely limited risk The clinical features of plague in North Amer ican cases differ in no way from those recognized and described for the infections connected with rat plague In its varying types it may range from a mild transient to a severe attack with or without buboes Aside from the benign plague or Pestis minor with prompt recov ery the carbuncular type the severe pneumonic form unaccompanied by buboes and the multiglandular fever with a prolonged course have been seen

Since human infections occurred in recent years in regions where it had not been previously seen diag nosis offered a number of difficulties Thus plague may

(8) Am J T p M d 936 J u ry 194

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(7) Lancet 1 66 666 May 4 1941

POLIOMYELITIS

Periodic Examination of Sewage for Virus of Poliomyelitis During poliomyelitis epidemics in 1939 the virus was detected in sewage collected in Charleston S C and Detroit All told in North America six positive tests were obtained with four samples of sewage These were among a total of 30 specimens examined which in addition to representing the aforementioned cities included samples from Windsor Ontario Buffalo and a rural area in Michigan The series included 22 tests on 11 postepidemic specimens from four large cities and the results of these tests were negative During an epidemic in Stockholm in 1939 a positive result was obtained by Kling These positive findings probably have epidemiologic significance but as yet they throw no crucial light on the pathogenesis of poliomyelitis and to understand them better it is still important to know more about normal conditions in respect to virus in sewage Accordingly data on sewage collected routinely over 15 months are presented by James D Trask and John R Paul[1] (Yale Univ) Periodic sampling in New Haven Conn and in New York City largely during nonepidemic periods is described

Of 45 monthly tests for the virus of poliomyelitis 36 were completed of these 35 were negative and 1 was positive Details of the positive test were as follows On September 19 the specimen was collected at the Manhattan Grit Chamber on September 21 the inoculum of 30 cc (the concentrate from 400 cc etherized sewage) was injected intra abdominally into a rhesus monkey which remained well until September 30 when it had fever October 1 it was tremulous and both legs were paralyzed October 2 it was prostrate and was killed Passage with glycerolated spinal cord was suc

(1) J Expe M d 75 1 6 J 1 194

be mistaken for tularemia or streptococcic infection Surgical procedures should be deferred until the nature of the infective process accompanied by a high fever of intermittent type pronounced toxemia and the formation of buboes has been established Case mortalities approximate 50 per cent for nonpneumonic cases

Clinical experience suggests use of antiplague serum in large doses Promising experimental results with sulfonamide drugs have been recorded In a recent human case however sulfathiazole did not influence the fatal course Until more adequate data are available it is recommended that a combination of sero-chemotherapy be tried

Live Plague Vaccine and the Results Following favorable results obtained with a live avirulent variant of the plague strain Tjiwidej in the plague immunization of rats and guinea pigs L Otten[9] (Pasteur Inst Bandoeng Java) applied the procedure to man During 1935 to 1939 he used the live vaccine in a vaccination campaign which extended to more than 2,500,000 subjects and in which nearly 10 000 000 vaccinations or revaccinations were done without harmful consequences to the health or life of the population The finding of avirulent variants of plague strains involves no particular difficulties and neither the production nor the application of live plague vaccine involves unpleasant surprises or dangers

[This very interesting experiment required considerable courage but it may prove to be of great value —Ed]

(9) Medede l v d d e t i lk g gndh n Nede l Ind 6 30 61 110 1941

tively large yields were obtained from glycerolated normal or infected tissues and from tissues that had been stored at -10 C for a few days Storage of normal frozen tissues for several weeks caused marked reduction of the amount of sedimentable nitrogen isolated Under these same conditions small but definite amounts of a high molecular weight material were isolated from the infectious extracts This material regularly produced poliomyelitis when 1 cc containing 5×10^{9} Gm nitrogen was injected intracerebrally into rhesus monkeys The purified virus sediment contains nitrogen phosphorus and carbohydrate gives Millon s test for protein and is precipitated by one third saturation with ammonium sulfate

[The concentration of poliomyelitis virus-containing materials including sewage etc has constituted an important advance in the study of the epidemiology of the disease because it makes possible the discovery of virus that would otherwise be missed — Ed]

Spread of Poliomyelitis Virus along Axons of Peripheral Nerves Hurst demonstrated that poliomyelitis can be produced in monkeys by injection of the virus into the sciatic nerve establishing the theory that poliomyelitis virus spreads via axonic pathways Thus has arisen the consensus that the virus has nearly an obligate affinity for naked gray fibers or for the gray fibered axis cylinders of peripheral nerves In accordance with this theory the virus might be picked up (1) by the axis cylinders of cranial nerves by which it would be brought directly to the medullary area (2) by the gray fibers of the sympathetic system along which it would spread to the somatic nerves and thence to the cord or (3) by the fibers of the parasympathetic nervous system whence it would pass along the vagus nerve to the medulla

Hurst s experiments were previously confirmed by John A Toomey and William S Takacs[3] (Western Reserve Univ) but in the course of their repetition four

(3) Am J D Child 63 467 473 M h 194

cessful in Macacus mulatta and the histologic lesions were typical Another monkey received only 20 cc unconcentrated sewage from the same sample and remained well during observation At autopsy no lesions were seen in its cord on microscopic examination This furnishes corroborative evidence that Gard's method of concentration is valuable

During the period in which the tests were conducted 11 cases of poliomyelitis were reported in the area served by the grit chamber from which the positive specimen was obtained There were four cases in July three in August and four in September the positive specimen was obtained in September Nine of these 11 cases were from a relatively small area If it is assumed that the virus detected had a direct human origin then either the heaviness of the contamination of the sewage or the amount of dilution which the virus tolerated are amazing

The positive result and its relation to cases of poliomyelitis reported add little to the knowledge of the pathogenesis of poliomyelitis but at least the data are of some special epidemiologic significance The nature of this is not yet obvious chiefly perhaps because it is not yet known whether the increase of cases precedes or follows an increase in the hypothetical basal level of the virus in sewage However as far as the data go they do not suggest that the virus is more or less evenly distributed throughout the year and that epidemics of paralysis are conditioned chiefly by variations in susceptibility which is postulated by Aycock s hypothesis of autarcesis in poliomyelitis

Studies on Purification of Poliomyelitis Virus Results of experiments on the preparation by high speed differential centrifugation of extracts of glycerolated or frozen normal and poliomyelitis infected medulla cords from rhesus monkeys are presented by Hubert S Loring and C E Schwerdt (Stanford Univ) Rela

( ) J Exp Med 75 395 406 Ap 1 194

was in Detroit in 1939 A total of 528 cases were recorded of which 255 were of the paralytic type Four cases occurred during pregnancy Although this occurrence is over four times the expectancy the number involved is too small to be considered conclusive However the finding is in line with other evidence presented suggesting that pregnancy may be one of the predisposing factors to paralytic poliomyelitis

This suspected selective occurrence is in accord with other selectivities which suggest that susceptibility to paralytic poliomyelitis may reside in a disturbance of some physiologic function which may be subject to fluctuations in the patient is endocrine in nature and is operative through effects on mucous membrane The known mucous membrane changes in pregnancy which are attributed to estrogenic changes and the experimental production of alterations in the genital and nasal mucosae of monkeys by the estrogens in view of the implication of the nasal mucosa as the portal of entry of poliomyelitis virus have formed the basis of two sets of experiments in an attempt to determine the nature of the factor responsible for susceptibility to paralytic poliomyelitis (1) tests of the effect of artificially induced changes on the susceptibility of monkeys to virus instilled intranasally and (2) comparative urinary estrogen assays on poliomyelitic patients and normal persons

Injection of estrogenic substance into castrate immature female monkeys was found to enhance resistance to virus instilled intranasally It is not known whether the particular preparation used the dosage and the manner of administration were responsible for changes that could be considered optimal so far as enhancement of resistance is concerned or whether such changes were entirely artificial and quite beyond what could be expected to exist naturally However since the experimental observations agree with epidemiologic implications it is believed that the artificially induced conditions may be considered as reflecting conditions of resistance

years later the disease did not develop in any of 10 monkeys inoculated via the sciatic nerve, although quadriplegia was produced in the same animals and other control animals a month later when they were all intracerebrally inoculated with the same amount and dilution of virus It was therefore necessary to obtain a plausible reason for these negative results or to abandon the evidence heretofore considered the foundation for the belief that the virus spreads by way of the axis cylinders

In seeking an explanation, it was found that the virus strain used had decreased in virulence since it had become necessary during the four years to increase its dose and concentration in order to produce quadriplegia in every instance Since the virus still produced experimental poliomyelitis in all monkeys into which it was injected intracerebrally it was thought that there may have been some quantitative changes in virulence of the strain which were not apparent on intracerebral inoculation That this was the fact was established by experimental comparison of the virus strain used by the authors with another subpassage specimen of the same virus strain obtained from a different laboratory The theory of axonic spread was thus upheld

Frequency of Poliomyelitis in Pregnancy Fifty six cases of poliomyelitis associated with pregnancy from the literature and from personal records are cited by W Lloyd Aycock[4] (Harvard Univ) The time of pregnancy when the disease occurred was unknown in two cases Only 9 cases were recorded in the first trimester of pregnancy whereas 19 were in the second trimester and 23 in the third Three cases occurred post partum Thus, the latter months of pregnancy appear to be chiefly concerned although the data for the first months may be discrepant The chance coincidence of the two conditions is roughly 1 in 1 000 poliomyelitis cases and 1 in 50 000 pregnancies The only outbreak in which the frequency of poliomyelitis in pregnancy has been studied

(4) New England J M d 5 405 408 Sept 11 1941

yielded virus Forty per cent of 35 stools from patients under 16 and 8 per cent of 38 stools from patients over 15 yielded virus Seventy one per cent of cords of 35 autopsied subjects under 16 and 31 per cent of those of subjects 16 and over yielded virus Second and third stools were collected from one to three months apart from five patients and one contact whose first stools contained virus All the repeat stools from the patients were negative while one positive stool was obtained from the contact two months after the first positive stool but a stool examined three months after yielded no virus

Natural History of Poliomyelitis Albert B Sabin and Robert Ward[6] (Univ of Cincinnati) report studies designed to determine by which secretions and excretions infective poliomyelitis virus is chiefly eliminated from the human body and to discover, if possible the origin of the eliminated virus Nasal secretions obtained from 22 paralyzed patients during the first two weeks of illness did not yield the virus in a single instance while the stools or enema returns of 9 of these patients contained readily demonstrable virus The nasal secretions of three 5 6 year old children with nonparalytic poliomyelitis were negative tests for virus in the stools of two of these patients were also negative No virus was found in the saliva and oral secretions of 20 patients Tests were made on the lower intestinal contents of only 10 of these the stools of 3 yielded the virus Tests for virus in large amounts of urine from 12 paralyzed patients were also all negative but no simultaneous studies were made on the stools of these patients

In the light of these findings the hypothesis that virus is present in the stools because it has been swallowed with nasal or other upper respiratory secretions becomes untenable and because it has been demonstrated in the walls of the alimentary tract its origin from these sites is much more probable However the negative results obtained with nasal secretions may be due to the pres-

(6) J Exp Med 74 1 9 D 1 1941

in the natural disease A small number of comparative urinary estrogen assays have been done on poliomyelitic patients and normal subjects Results showed a higher excretion of estrogenic substance by the poliomyelitic subjects

It is not known why if administration of estrogen protects castrate monkeys the higher excretion of estrogen found in poliomyelitis cases and characteristic of pregnancy should not confer a similar benefit However the hormonal status of the pregnant woman differs from that of the nonpregnant as well as the castrate animal in a variety of ways Thus pregnancy is dominated more by the corpus luteum hormone than by estrogen Pituitary growth hormone secretion, as well as prolactin is enhanced during pregnancy In short the end effect of several interacting variables one of which may be increased estrogen may actually differ from that of increased estrogen alone In this particular case, administration of estrogen to castrate animals approaches the latter condition whereas conditions in the natural disease involve the interaction of a number of hormones of which increased urinary output of estrogen may be only one manifestation

Occurrence of Poliomyelitis Virus in Autopsies Patients and Contacts John F Kessel, Frederick J Moore, Fred D Stimpert and Roy T Fisk (Univ of Southern California) report recovery in monkeys of poliomyelitis virus from 50 per cent of spinal cords 10 per cent of olfactory bulbs 50 per cent of tonsil adenoid tissue and 26 per cent of the colon contents of autopsied subjects and from the stools of 20 per cent of patients and 5 per cent of contacts Tonsil adenoid tissues or colon contents were positive in 73 per cent of autopsied subjects with positive cords Twenty two per cent of stools from patients with paralysis and 19 per cent from patients without paralysis yielded virus Twenty per cent of stools from males and 22 per cent from females

(5) J Exp Med 4 601 609 Dec 1 1941

urinary bladder it nevertheless seems advisable to await actual tests with bladder tissue and further studies on children under 8 before reaching a final decision about the noninfectiousness of urine

Experimental Poliomyelitis Infection —Albert B Sabin and Robert Ward[7] (Univ of Cincinnati) report experiments in which eight rhesus monkeys with experimental poliomyelitis following intrasciatic inoculation of M V virus were used to study the extent of virus spread in the central and peripheral nervous systems and the question of its elimination in the nasal secretions Tests on nasal secretions collected on absorbent cotton plugs daily and continuously from the moment of inoculation to the end of the disease failed to reveal virus No virus was found in the olfactory bulbs nasal mucosa tonsils and adjacent pharyngeal tissue salivary glands adrenals superior cervical sympathetic ganglions abdominal celiac ganglions and small intestine

Elimination of virus by the nasal route was not one of the consequences of poliomyelitis infection resulting from invasion of the M.V virus by way of a peripheral nerve in rhesus monkeys

No indiscriminate widespread dissemination of virus occurred in the central nervous system of the intraneurally inoculated rhesus monkeys nor did the virus spread outward sufficiently to involve the collateral sympathetic ganglions or the collections of nerve cells in various peripheral tissues Under certain circumstances therefore presence of virus in these ganglions and tissues may be used as an index to the portal of entry of the virus

(7) J Exp M d 75 107 117 J n 1 194

ence of an inactivating substance and need not necessarily indicate absence of virus If there is such a substance it might be suggested that it should have been effective in preventing local multiplication in the nasal mucosa, or if it arises in response to infection, that its presence would thus militate against the spread of infective virus by means of nasal secretions However, studies by the authors on the pattern of virus distribution in the human body suggest that the virus neither multiplied in nor invaded the nervous system by way of the nose because while it was readily demonstrable in the pharyngeal and intestinal tissues it was not present in the nasal mucosa or the olfactory bulbs in the cases studied

For practical purposes therefore it appears that in human paralytic poliomyelitis the secretions as they are expelled from the nose or expectorated from the mouth are probably free from infective virus However since the virus has been demonstrated in the pharyngeal tissue post mortem as well as in a certain number of pharyngeal wall washings it is necessary to determine whether virus that may be present in the pharynx would under natural conditions be swept into the esophagus or might also find its way into the oral secretions and be expelled with them Since the authors recently observed that in cynomolgus monkeys which had developed poliomyelitis after oral feeding of the virus one can find the virus in appreciable amounts in the buccal mucosa and tongue as well as in the pharyngeal wall and oropharyngeal washings it would be well to await similar tests on human beings post mortem as well as further studies of oral washings particularly during the first days of the disease in young children before attempting to form any concept concerning the role of the mouth as a site of exit of virus Although tests with large amounts of urine were all negative and while the pattern of virus distribution in the human body indicates that there is not sufficient centrifugal progression of virus to permit its invasion of the

increase in the concentration of this antibody It may be assumed that the initial or prerelapse titer was the result of previous hemolytic streptococcus infection and that the rise in titer accompanying the relapse is due to invasion of the body by new strains of streptococci Comparable statements can be made concerning antifibrinolysins with the added observation of Boisvert that in his experience these antibodies seem to persist longer in the blood of rheumatic children than in those with other hemolytic streptococcus infections Also supporting the general assumption of the inciting role of streptococci in rheumatic fever is the prophylactic action of sulfanilamide

With the theory of a close relationship between hemolytic streptococcus infections and rheumatic fever certain etiologic factors become more lucid The seasonal incidence of the disease in the north temperate zone follows that of the streptococcus carrier rate with a lag of about a month between the peak of the two curves The geographic distribution of rheumatic fever also runs roughly parallel with the streptococcus carrier rate In Pomales-Lebron s tabulation of different observations on pharyngeal hemolytic streptococcus carrier rates in different parts of the world a low incidence was found in Puerto Rico the Virgin Islands Alabama Labrador and Spitzenberg These regions with widely different climates have a low rheumatic fever rate The converse is true in New York Chicago or London The higher rheumatism rate in children of poor or crowded families is likewise rationally explained on the great probability of streptococcus infections being distributed among most of the family compared with those in better circumstances

[There seems little doubt of the frequent connection between hemolytic streptococcus infections and rheumatic fever but the relationship may be only a predisposing one as otherwise streptococcus infections would be more constantly followed by rheumatic fever Hemolytic streptococci may also act in a synergistic manner with another specific agent —Ed]

Nature and Etiology of Rheumatic Fever are discussed by Homer F Swift[8] (Rockefeller Inst) Rheumatic fever appears to wax or wane under certain geographic and atmospheric conditions It has been noted frequently that the disease is much more prevalent in cold northern climates than in the warm southern zones Seasonal variation also occurs within the different latitudes for it is common experience in most northern cities to see a marked fall in the incidence of the disease as summer arrives Many patients with continued rheumatic activity throughout the winter show marked improvement in warm weather in much the same way as has been observed when they move from a cold northern to a tropical climate Economic status within a given area is also significant for the disease is more common among those poorly housed clothed and fed Heredity has been statistically implicated for multiple cases are often found in families but a hereditary tendency without an inciting agent would probably not result in rheumatic fever

The great weight of evidence leaves little doubt of some connection between hemolytic streptococcus infections and rheumatic fever Arguments against this theory are based on clinical observation or on incomplete bacteriologic studies Good immunologic evidence connects rheumatic fever closely with hemolytic streptococcus infections Thus numerous observers have shown that the so called antistreptolysin O titer in the serum of rheumatic patients is as high or higher than in that of patients with known hemolytic streptococcus infections While many rheumatic fever patients in the recovered or quiescent period have in their serums antistreptolysin titers distinctly in the abnormal range a recurrence of rheumatic fever is usually accompanied by an additional

(8) Cinc at J Med 73 58 4 April 1942

subcutaneously are 650 2 500 10 000 30 000 and 100 000 skin test doses If the patient has a severe reaction to the initial dose or to the skin test subsequent injections should be decreased in amount and the number of *injections increased Adrenalin is sometimes given with* the toxin in 0 2 to 0 3 cc doses of a 1 1 000 solution In a highly sensitive individual one may start with one fourth and increase to one half of the original recommended dose the next time going back to the initial dose If at any time there is a marked reaction it might be advisable to revert to the last standard dose and then to start again with a quarter of that recommended Each such susceptible person is an individual problem

Seventy six nurses were admitted with scarlet fever who had had negative Dick reactions from one day to five years prior to contracting the disease They constituted 2 per cent of the negative reactors Despite previous reports they were again tested Eight reactions could not be read accurately because of the rash 25 nurses had lost their immunity and were definitely positive reactors on admission while 43 were still negative This would give a corrected morbidity of 1 per cent in the exposed negative reactors

There are many reasons why a Dick test may be erroneously negative This could explain some but certainly not most of aberrant results A negative reaction may occur if the test material is not up to standard because it has not been kept properly and in accordance with the specifications

There is only a minute amount of toxin in the skin test dose This may be easily neutralized or destroyed by some factor—soap alcohol iodine etc The skin test is a quantitative one indicating the presence of a certain amount of antitoxin in the blood stream thus quantitative exposure greater than the usual may initiate scarlet fever in an individual who has protection against the ordinary doses of antigen to which he would customarily be exposed

Scarlet Fever Immunization John A Toomey[1] (Western Reserve Univ) describes experiences following active immunization of 1,329 susceptible nurses Toxins in the old standard doses of 500, 2,000, 8,000 25 000 and 80 000 units as recommended by the Scarlet Fever Commission were given to 1 273 Larson's vaccine to 41 and toxin made from stock streptococci to 15 Not all of the 1 273 nurses received the recommended full five doses 155 had one to four doses and 1,118 five or more Of the 1 273 1 181 became negative reactors and 92 were still positive

Sixty five of the susceptible nurses contracted scarlet fever 49 becoming ill during immunization Discounting these 49 there were 16 nurses or a little over 1 per cent of the total 1 273 immunized who developed the disease On hospitalization eight of these nurses had acquired some immunity and were negative reactors to the Dick test eight were still positive Seven had mild attacks three moderate and five severe diagnosis in one case was questionable The reactions to the test bear no relation to the severity of the subsequent attacks of scarlet fever Actually eight nurses had not been immunized thus there remained eight failures

Reactions to scarlet fever immunization are either local or general or both Local reactions include redness induration and sometimes an erysipeloid inflammatory reaction around the point of injection lymphangitis local adenitis pain on activating the arm fever etc General reactions include malaise nausea headache high fever a scarlatiniform rash vomiting diarrhea adenitis arthritis, etc Reactions occurred at some time or other in 131 of the nurses injected These included 38 local and 326 general reactions

The amounts of skin test doses of toxin now recommended by the Scarlet Fever Commission and injected

(1) Ann. Int. Med 15 959 973 D mbe 1941

Scarlet Fever Immunization Reactions subsequent to immunization of 62 children and 6 adults with scarlet fever streptococcus toxin (Lederle) are described by Clarence G Thompson (Norwich) Age range of the children was 6-15 years Immunization was accomplished by injection of 650 2 500 10 000 30 000 and 100 000 skin test doses at weekly intervals Reactions were classified as mild when only a local reaction with slight constitutional symptoms occurred as moderate when in addition to localized redness there occurred slight or moderate fever malaise vomiting and occasional joint pains and as severe when the subject had to go to bed because of fever malaise joint pains sore throat or excessive vomiting

Following the first dose of 650 units there occurred 20 mild 40 moderate and 8 severe reactions 2 of the severe reactions were in adults The second dose of 2 500 units evoked 40 mild 18 moderate and 10 severe reactions The third dose of 10 000 units elicited 45 mild 15 moderate and 8 severe reactions The fourth dose of 30 000 units was followed by 50 mild 12 moderate and 6 severe reactions while the fifth dose of 100 000 units brought forth 55 mild 11 moderate and only 2 severe reactions None of the adults took the fifth dose

Of those with severe reactions two of the children who reacted to all five injections came from poor families were badly nourished and had poor resistance Two adults experienced severe reactions following all four doses this is considered in keeping with the severity and frequent complications of childhood diseases in adults No later reactions occurred

Management of Scarlet Fever Contacts is outlined by Paul S Rhoads Winston H Tucker and Benjamin Rapaport[3] (Northwestern Univ) The Dicks for several years have recommended the following procedures when scarlet fever breaks out in a home or an institution

( ) C t t M J 5 736 740 O t b 1941
(3) J A M A 117 1063 1 6? S pt 7 1941

In doing a Dick test the skin must be dry and cleansed of alcohol and other disinfecting agents Needles and syringes must be dry and should not be boiled in tap water The dose of toxin must be accurately measured The injection should be into the skin and the reaction should be read at the proper time

Some feel that all that is accomplished by giving scarlet fever toxin is immunization against the toxin that produces the rash They feel that immunized persons may still become ill from streptococci which cause scarlet fever Some believe that the number of colds sore throats etc in this group is increased Toomey s observations however indicate that there has been no increase in the number of nurses who have contracted scarlet fever or who have contracted streptococcic sore throat rather there has been a definite decrease

The recent Army Bulletin no 81 recommends that active immunization should be given to nurses with positive reactions to the Dick test and to orderlies assigned to care for scarlet fever patients It was not recommended for general use to the surgeon general because there is a high percentage of immune subjects among adults and because at least five or more injections are usually required to produce immunity '

Susceptible young adults in contagious disease hospitals contract the disease because of massive exposure etc *and it has been proved repeatedly that these individuals can be protected* It is equally obvious that where there is crowding and disease occurs as in the army cross infections will follow It is not clear why susceptible exposees in the army should not be immunized

In pediatric practice the only reason the vaccine may not be used is because of the reactions but physicians especially pediatricians can easily immunize their patients especially if they appreciate the reactions and avoid them by injecting a greater number of smaller doses

2 A contact may be found susceptible but not infected He should start active immunization at once so that he will be protected when the convalescent carrier returns but need not be quarantined as he will not spread the illness

3 A contact may have a culture positive for hemolytic streptococci but a negative Dick reaction He needs neither passive nor active immunization but should be kept isolated from susceptible persons because the streptococci which he harbors must be regarded as scarlatinal streptococci until proved otherwise

4 A contact may have a negative culture and a negative cutaneous reaction He needs no treatment but should be kept from carriers so that he will not become one

Cardiovascular Disorders in Scarlet Fever are reviewed by Conrad Wesselhoeft[4] (Harvard Univ) The vascular disturbances of the eruptive stage consist in dilatation of the peripheral capillaries of the skin—the exanthem—and of those portions of the mucous membrane involved in the exanthem Thus the chief characteristic of the disease is brought about by the action of the toxin on the peripheral capillaries From this it may be expected that the heart as a highly specialized organ of this vascular system would be susceptible to attack by the toxin Actually the heart is under certain circumstances peculiarly susceptible to the scarlatinal toxins but in most cases this susceptibility leads to no more harm than the rash itself

Conversely serious cardiovascular disorders may follow scarlet fever However observations indicate that they are relatively infrequent as compared with those following rheumatic fever and chorea Most valvular lesions found in the course of scarlet fever can be traced to previous rheumatic or choreic infection

The endocarditis that originates from the hemolytic streptococcus of scarlet fever is a result of blood stream

(4) N w E gl d J M d 4 94 947 M y 9 1941

(1) Isolation of the patient, (2) Dick tests on all contacts including adults (3) cultures of material from the nose and throat of all contacts using blood agar plates (4) temperature readings and inspection of the throat and the upper part of the trunk of all contacts

When inspection and temperature reading suggest the imminence of scarlet fever passive immunization may be produced at once by injection of a prophylactic dose (a minimum of 150 000 original neutralizing units) of scarlet fever antitoxin or an adequate dose of scarlet fever convalescent serum It is safest never to give less than 40 cc convalescent serum for this purpose although smaller doses are sometimes effective It is rarely necessary to use either agent If no evidence of beginning illness in the contacts is found, it is safe to wait 24 hours at which time the results of culture and cutaneous tests are known Reading of the temperature and inspection of the skin and mucous membrane are again made and persons found susceptible or showing signs of beginning illness are treated in the manner outlined However one week later their active immunization with five graduated doses of scarlet fever toxin (or more injections in less rapidly increasing doses) is begun so that they will be immunized by the time quarantine is lifted Among those found not to be ill the following situations may be present

1 A contact may be found susceptible and harboring hemolytic streptococci If he can be kept under daily observation he may start active immunization at once so that he will be immunized completely or partially by the time the quarantine is lifted and contact with the convalescent patient who is usually still a carrier of scarlatinal streptococci is resumed He must also be isolated from susceptible persons, because he is a carrier and hence capable of spreading scarlet fever If he cannot be observed daily it is safer to give him passive immunization at once but to begin active immunization one week later

childhood and therefore many potential rheumatic patients develop scarlet fever before their first attack of rheumatic fever Furthermore older patients are less likely to develop valvular disease than children in the course of rheumatic fever attacks Consequently these two factors reduce the chances of rheumatic endocarditis developing during scarlet fever If the valves are already damaged by a previous attack of rheumatic fever *the endocarditis cannot be* said to have originated with the scarlet fever but is merely brought into renewed activity by it

A true severe myocarditis such as occurs in diphtheria is rare in scarlet fever In most cases severe myocarditis is due to a mixed infection with the diphtheria bacillus a not uncommon complication This point should always be investigated when severe myocarditis develops in scarlet fever

Pericarditis may occur as the result of bacteremia in which case streptococci are found in the pericardial fluid Here the pathology is no different from that found in any other similar infection with hemolytic streptococci This also applies to the rheumatic form of pericarditis The incidence of pericarditis in scarlet fever has been found to be 0 09 per cent

Endocarditis and pericarditis of rheumatic origin require the usual treatment outlined under rheumatic fever with salicylates and digitalis when indicated However patients with a rheumatic history who develop pain and swelling in the joints during scarlet fever may not respond well to salicylates Maximum doses are frequently necessary to control pain Digitalization on the other hand may be relied on when indicated in cases of old valvular lesions with congestive failure or auricular fibrillation

In endocarditis and pericarditis of bacterial origin sulfanilamide should be given with maintenance of high blood levels If the bacteremia has proceeded to a vegetative endocarditis prognosis is grave In rare

infection and constitutes a bacterial endocarditis Furthermore in scarlet fever such blood stream infection is apt to follow a local pyogenic process in the mastoid cells associated with lateral sinus thrombosis But even with a blood stream infection, such an endocarditis occurs rarely In fact its infrequency in cases of bacteremia suggests that a previously damaged valve may be necessary The commoner form of endocarditis seen in scarlet fever is of rheumatic origin

Statistical study of 192 678 hospital cases of scarlet fever showed an incidence of endocarditis of 0 51 per cent Exclusion of those cases with the characteristics of rheumatic fever shows that true scarlet fever endocarditis with vegetations and permanent damage is extremely rare

Both scarlet fever and rheumatic fever are intimately related to the streptococcus Allergic hypotheses have been advanced to explain the symptoms in each The close clinical and immunologic relation of the hemolytic streptococcus to rheumatic fever has been emphasized In scarlet fever the erythrogenic toxin is the product of certain strains of hemolytic streptococci although some still believe that a virus is implicated In rheumatic fever a nonhemolytic streptococcus is incriminated in much the same way as the streptococcus in scarlet fever before the discovery of the Dicks Recent evidence supports the hypothesis that a virus is associated with the streptococcus in rheumatic fever Also it is conceded that streptococcic infection predisposes the tissues to a latent rheumatic fever infection If this hypothesis is correct infection with scarlet fever might likewise activate any latent rheumatic fever element clinical evidence supports this In the light of this knowledge an established valvular defect developing late after scarlet fever should be considered of rheumatic origin

In connection with the rheumatic origin of endocarditis in the course of scarlet fever it should be remembered that scarlet fever is a disease largely of early

Classification of Staphylococci Emma S Moss Gretchen Vitter Squires and Anne C Pitts[6] (Charity Hosp New Orleans) compared the coagulase test with others used for the classification of staphylococci particularly with regard to pathogenicity The coagulase activity of staphylococci suggests itself as a possible index of pathogenicity especially since it can be performed with sufficient rapidity to answer the requirements of chemotherapeutic and serotherapeutic methods

The authors conclude that all coagulase positive strains of staphylococci are pathogenic but that a negative coagulase test does not exclude pathogenicity Pigment production is strong evidence of pathogenicity but nonpigment producers may also be pathogens Although mannitol was fermented by a high percentage of pathogenic strains it was also fermented by nonpathogenic strains Thus it is less valuable as an indication of pathogenicity than the coagulase test because the latter rendered no false positives The high percentage of hemolytic albus strains completely excludes this method as a means of determining pathogenicity Failure to produce abscesses in white mice does not exclude pathogenicity in man although no coagulase negative strains produced abscess

Treatment of Severe Staphylococcic Infection with Specific Type A Antibacterial Serum Harry G McNamee[7] (Philadelphia Gen l Hosp) reports results of treatment of 18 patients with verified staphylococcic septicemia 1 with osteomyelitis and transient bacteremia and 3 with pneumonia without positive blood cultures Treatment consisted of administration of type A antiserum and whatever supportive care and surgical measures were indicated In many sulfon

(6) Am. J Cl P th 11 857 863 D c mbe 1941
(7) A n S g 115 308 317 F bru ry 194

cases, recovery has occurred, and immunotransfusion along with sulfanilamide may benefit Tapping the pericardium may be resorted to, but should be attempted only by experienced persons

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SMALLPOX

Chorio Allantoic Membrane Infection as Diagnostic Test for Smallpox is reported by S W Bohls and J V Irons[5] (Austin, Tex) Eighteen isolates of smallpox virus were propagated in the chorio allantois of embryonated hen eggs in an environment free from bacteria and fungi Characteristic lesions consistent with those of smallpox appeared in less than 48 hours and were applicable in the laboratory diagnosis of smallpox The presumptive positive result was available usually on the third day Four days were required for the completed negative test Final identification of the lesions required application of additional cultural microscopic histologic or serologic methods

Tests with chickenpox specimens gave negative results The chorio allantoic infection test should be carefully applied in the light of clinical findings, and a negative result should not justify withholding smallpox vaccination

(5) Am J Pub He lth 3 300 306 M h 194

and blood Serum treatment started the fifteenth day of illness consisted of 120 cc given over three days

Five of the surviving patients developed serum sickness manifest as urticaria and in two joint pains This condition responded promptly to symptomatic treatment Skin tests to the type A carbohydrate to measure the adequacy of serum treatment were positive in five of the six patients on whom they were performed

Of the 12 who died 7 had endocarditis and 1 each had pneumonia pericarditis sinus thrombosis sinusitis with metastatic pneumonia and undetermined septicemia Analysis of the fatal cases suggests that the rate of recovery in this study may be an inaccurate expression of the true capacity of the antiserum For example cardiac complications in 8 of 22 or from the point of view of deaths 8 of 12 indicate the particularly abnormal run of patients in this study Also 9 of the 12 deaths occurred within five days following use of serum In the light of such a disproportionately large number of patients with hopeless prognosis it may be that the antiserum possesses a greater therapeutic efficiency than is actually observed in this study

[This interesting report indicates that staphylococcus antibacterial serum is valuable in combating severe staphylococcic infections —Ed]

Incidence of Potentially Pathogenic Staphylococci in the Nose and on the Skin of Healthy Subjects A N Smith[8] reports examination of 100 healthy individuals for potentially pathogenic staphylococci in the nose and on the skin Organisms isolated were tested for pigment formation and fermentation of mannitol and coagulase formation the last being the most accurate index of pathogenicity Thirty two per cent of the individuals examined were nasal carriers and 5 per cent skin carriers

The significance of the work in relation to infection of wounds is evident especially in the light of the previ

(8) J Roy Army M Corp 6 341 344 J 1941

amide treatment had been used prior to serum administration but this appeared to be largely ineffective

Five males and five females, aged 20 months to 43 years treated with serum eventually survived In four the septicemia originated from osteomyelitis in one further complicated by clinically recognizable myocarditis confirmed by electrocardiographic studies In four others the infection was predominantly pulmonary In two the pneumonic process was primary, although postoperative in one, and in two others the pneumonia was secondary to a surface lesion The effect of serum in two of these patients was especially impressive Thus in one, the pneumonia appeared two days after herniorrhaphy Recognized as being of staphylococcic etiology 54 Gm sulfathiazole was given in seven days but the infection intensified with formation of multiple pulmonary abscesses Prognosis seemed hopeless but serum therapy was started and 260 cc was given intravenously over seven days with recovery The other patient had typical primary staphylococcic bronchopneumonia confirmed by roentgen and sputum studies which yielded pure culture of Staphylococcus aureus Serum treatment was delayed eleven days because of sulfathiazole therapy (74 Gm total) then two intravenous injections of serum were given 60 cc the eleventh day and 40 cc the twelfth day Twelve hours after the second injection the temperature fell to normal and remained

In the two other surviving patients the infection was primarily in the meninges One was a woman who, following an injury showed all the signs of typical meningitis Spinal fluid yielded staphylococci on culture and the cell count and protein content were characteristic of purulent meningitis Serum treatment started the sixth day consisted of two injections The spinal fluid became sterile several days later, recovery was complete In the other also a woman, the chief clinical signs were those of meningitis with positive cultures of hemolytic Staphylococcus aureus from both spinal fluid

rheumatic arteriosclerotic or hypertensive heart disease only one patient made a recovery

Metastatic lesions were common and occurred in 82 per cent of cases When metastatic lesions failed to ap pear the course was unusually rapid and death occurred 2 10 days after initial symptoms In patients who re covered the illness ran a protracted course because of metastatic infection

When recovery takes place the blood is cleared of organisms and either the focus of infection which is re sponsible for the bacteremia is drained or a metastatic abscess is localized and drained This is observed more frequently in patients under 40

The following methods of treatment are recommended (1) administration of antitoxin for neutralization of circulating toxin (2) blood transfusions (3) surgical drainage of all foci of infection and (4) use of large amounts of sulfapyridine or sulfathiazole

[The caution against rupturing local defense infiltration sur rounding foci of staphylococcus infection should be emphasized We have long opposed early incisions of boils and furuncles —Ed]

TETANUS

Clinical Tetanus Hyman I Vener and Albert G Bower[1] (Univ of Southern California) describe treat ment and results in a series of 100 patients Twenty nine deaths occurred a gross fatality rate of 29 per cent Twelve patients died within the first 24 hours of hospitalization Among the 88 patients who survived longer than 24 hours 17 deaths occurred a net mor tality rate of 19 3 per cent Approximately 50 per cent of patients were admitted with a history of symptoms for three days or longer and frequently in severe con vulsions Schematic management of a hypothetical case is outlined time intervals are noted for clarity

TREATMENT—The patient is admitted at 9 00 a m The history is obtained and physical examination is performed

(1) J A M A. 116 16 7 1631 Ap 1 1941

ous work by Devenish and Miles, who showed that organisms could be grown from the inside of operating gloves following a surgical procedure

Significance of Bacteremia Caused by Staphylococcus Aureus David Skinner and Chester S Keefer[9] (Harvard Univ) describe a study of 122 cases observed over a seven year period All patients had demonstrable bacteremia on one or more occasions and the clinical course was entirely consistent with severe infection Twenty two recovered (mortality 81 97 per cent) There were four common portals of entry the skin 57 cases respiratory tract 30 bone 11, and genito urinary tract 11 In 12 portal of entry was unknown

Significant in the pathogenesis of bacteremia was rupture of the local defense mechanism by incision of an abscess In 21 such cases there were only 2 recoveries In most cases the infection was localized in the skin in the form of a furuncle or carbuncle which usually had been incised shortly before the development of bacteremia Two of these patients had diabetes and one arteriosclerosis Bacteremia following rupture of local defense mechanism occurred at all ages an age incidence paralleling that of the entire series Pneumonia developed in seven and in six the infection spread by direct extension from the primary focus to the surrounding tissues This emphasizes the dangers of rupturing the local defense mechanism of the body once an abscess has formed and the necessity of great care in draining such an abscess without injury to the surrounding tissues

There were 15 cases of wound infection with associated bacteremia all fatal Bacteremia following trauma without interruption of skin continuity was observed in 19 cases, with 11 deaths The presence of debilitating diseases was significant in both development and outcome of the bacteremia Of 9 patients with diabetes mellitus 9 with arteriosclerosis and 16 with

(9) Arch Int Med 68 851 875 N embe 1941

antitoxin 15 gr methenamine is given intravenously Methenamine is thought to act by alteration of the choroid plexus allowing greater permeability to antitoxin

At 2 00 a m if no reaction has ensued from the first intravenous use of antitoxin 20 000 additional units is given intravenously in 300 to 500 cc physiologic sodium chloride solution If a febrile reaction follows the first intravenous dose of antitoxin the second is held in temporary abeyance If anaphylaxis severe chill or other untoward reaction occurs the second intravenous dose of antitoxin is not given

Approximately 12 hours after the second intravenous dose the final 40 000 units of antitoxin is injected deep intramuscularly just proximal to the previous site of injection Should the second intravenous dose of antitoxin have been omitted the final intramuscular dose is increased to 60 000 units

Fifteen gr methenamine is given intravenously as before 10 to 12 hours after each intramuscular injection of antitoxin

A total dose of 200 000 units of antitoxin has now been administered within 30 to 36 hours after admission Additional large doses are not given unless the patient has a relapse (No patient in this series received more than 230 000 units) The ordinary prophylactic dose of 1 500 units is given subcutaneously at four to five day intervals to maintain desensitization If future orthopedic or other surgical measures are contemplated these desensitizing doses are continued for two weeks after surgical intervention If this precaution is not observed relapses occur

If a patient is especially sensitive to horse serum or is subject to allergy or previously has received prophylactic antitoxin followed by serum reaction and tetanus the cisternal and intravenous procedures are omitted In this event all antitoxin is divided into two intramuscular injections of 100 000 units each given at 12 to 18 hour intervals and followed by methenamine as described

The patient is given all the fluids orally that can be tolerated without causing severe convulsions If he is unable to swallow dextrose saline solution or combined dextrose and saline may be given intravenously In the average case a maximum of 1 500 cc daily suffices Excessive fluids may induce pulmonary edema hypostatic pneumonia or cardiac dilatation

Good general nursing care with minimal disturbance of the patient is essential

[While an undue hypnosis is undesirable it is also true that insufficient sedative may result in a fatal convulsion It is also

with minimal disturbance Infectious focus is found if possible and a serum test is done on the skin for sensitivity

At 9 30 a m chloral hydrate, 10 30 gr, depending on size and age of patient is given orally If the patient is unable to swallow, the drug is given in combination with the same amount of calcium bromide by retention enema Deep narcosis must be avoided because of possible attendant adverse metabolic changes Occasionally the dose cited may have to be repeated or else supplemented with 3 to 5 gr soluble phenobarbital given intravenously If possible, one hour should elapse before other treatment is begun

At 11 00 a m 20 000 units of antitoxin is injected completely around the lesion Frequently, if wound location permits antitoxin injection is preceded by local procaine hydrochloride infiltration After 45 to 60 minutes the focus is incised widely or excised thoroughly whichever procedure is applicable Excision must be done within the area encircled by antitoxin Debridement must be complete The area is treated subsequently as though infected, and hot potassium permanganate compresses are applied In some instances if a finger or toe is involved in the focus, the digit is amputated Here individual judgment applies

Before any surgical intervention 60 000 units of antitoxin is injected deep intramuscularly girdling the extremity of the part involved when possible injection is made at the junction of the upper and middle thirds of the infected part s proximal portion

At 2 00 p m if sedation is sufficient, cisternal therapy is initiated, if necessary further sedation may be given by methods previously indicated Under aseptic technic cisternal puncture is done about 10 cc fluid is removed and 20 000 units of antitoxin previously warmed to body temperature is injected slowly by gravity After this rectal temperature may become elevated to 102 to 106 F within a few hours but usually subsides within 8 to 10 hours Hourly readings are made and when rectal temperature has receded to about 102 F the next step is performed

At 10 00 p m 40 000 units of antitoxin diluted in 300 to 500 cc physiologic solution of sodium chloride is administered regardless of patient s age or size Flow is by gravity and is slow at least one hour being allowed for completion To forestall anaphylactic shock 5 minims epinephrine is given hypodermically five minutes preceding intravenous injection this dose is repeated midway in and at the completion of injection

At 1 00 a m., two hours after intravenous injection of

dose and another dose at the time of injury The United States Navy and Marine Corps use a similar plan except that alum precipitated toxoid is given and the basic course consists of two injections four weeks apart Demonstration that simultaneous injection of tetanus toxoid with diphtheria toxoid or with typhoid paratyphoid vaccine or with both is not only feasible but actually results in a higher antitoxin titer is an important contribution Tetanus toxoid can easily be given during the almost universal immunization against diphtheria in infants and may be given advantageously to those being immunized against typhoid fever

[It should be kept in mind that alum precipitated toxoid contains a greater proportion of foreign protein than plain toxoid — Ed]

Localized Action on the Spinal Cord of Intramuscularly Injected Tetanus Toxin George H Acheson Oscar D Ratnoff and Emanuel B Schoenbach[3] (Harvard Univ) studied local tetanus limited to one leg in cats after intramuscular injection of tetanus toxin It was observed that the electric and mechanical response of the affected muscle after a single stimulus to the intact sensory motor nerve was greater in amplitude and duration than the response of the corresponding muscle of the unaffected leg This augmented muscular response was associated with an augmented response arising from the ipsilateral portion of the spinal cord while the contralateral part of the cord was unaffected The augmented muscular response was abolished when the reflex arc was broken but the augmented response in the spinal cord was independent of changes in the muscle the neuromuscular junction the afferent and efferent peripheral nerves and the dorsal root ganglions

The augmented spinal response develops in the absence of the peripheral signs of local tetanus Hence the pathogenesis of the altered state in the spinal cord is independent of the peripheral effects of the toxin In

(3) J E p Med 5 465 480 M y 194

possible that the intravenous injection of antitoxin should have an earlier place on the program —Ed]

Problems Concerning Active Immunization against Tetanus are discussed by Harris B Shumacker Jr and Austin Lamont[7] (Johns Hopkins Hosp) Of the two types of toxoid available for active immunization plain and alum precipitated the latter has been found to produce a better antitoxin response Nevertheless technics have been worked out with both types which result in apparently satisfactory antitoxin production A single injection of toxoid causes no demonstrable production of a significant amount of antitoxin in human subjects The first dose appears to sensitize or prepare the subject so that he will respond to subsequent injections with rapid and pronounced antibody production Within two weeks after a second and within a week after a subsequent injection antitoxin titer rises to an almost certainly protective level The consensus is that a relatively long interval is preferable between the two or three doses constituting the basic course of immunization The recommended interval varies from three weeks to three months

The general plan of immunization consists of two or preferably three injections of toxoid given at long intervals never less than four weeks and a reinjection at time of injury In certain instances it may be wise to keep the titer high in advance of possible injury by administration of toxoid at 6 to 12 month intervals For such purposes intranasal instillation of refined toxoid (topagen) is satisfactory The French army used three doses of the triple vaccine given at three week intervals the British army two doses of plain toxoid at six week intervals The United States Army uses three injections of plain toxoid three to four weeks apart a stimulating dose at the end of the first year another during the month before departure for combat zones unless this takes place within six months of the stimulating

(7) Surg Gynec & Obst 74 433 438 Feb 16 1942

The temperature fluctuated between 101 and 103 2 F during the first three hospital days On December 4 half an ampule of lyovac antitularemic serum was given intravenously at 12 30 p m and the remainder at 8 30 p m on the same day There was no reaction other than profuse diaphoresis after each dose of serum and a rise in temperature to 104 F after the second dose During the night temperature fell to 103 F

On December 5 another ampule of lyovac was given intravenously in two doses at 4 00 and 9 00 p m respectively each dose being followed by diaphoresis and a drop in temperature from 103 2 to 98 2 F on the following day The temperature fluctuated between 98 2 and 101 4 F on December 7 and 8 and at dismissal on December 9 was 98 2 F

Medication other than the antitularemic serum was symptomatic during hospitalization Convalescence following discharge was rather slow the patient complaining of dry cough and daily temperature rise to 100 F Stereoscopic roentgenograms taken on January 21 revealed a small amount of fluid in the left base with pleural thickening considerable bilateral peribronchial thickening and many old glands about the hili with no evidence of recent activity

The pustule on the patient s finger slowly disappeared without suppuration after administration of the antiserum Final diagnosis was tularemia of the ulceroglandular and pulmonary form

Antitularemic Serum Foshay s advocacy of antitularemic serum for treatment of tularemia in man has prompted renewal of the search for specific protective bodies in antitularemic serum The presence of high titer protective antibodies in immune serum is essential for satisfactory action against pneumococcic and meningococcic infections As far as is known protective antibody is the only agent which brings about curative action following passive transfer of any immune serum Thus it would seem logical in the case of Bacterium tularense to establish whether or not a protective serum could be developed as measured in experimental animals In other words until it is proved that Bacterium tularense is unlike other bacteria in this respect only from immune serum containing adequate protective antibodies would successful treatment be anticipated The fact that apparently lasting immunity follows the in

local tetanus therefore the toxin injected intramuscularly acts selectively on the cord segments which supply the innervation of the injected area The augmented *spinal response may be prevented by section of the* nerve trunks supplying the area of injection prior to injection of toxin It is concluded that in local tetanus the toxin is carried to the spinal cord by way of peripheral nerves

TULAREMIA

Tularemia and Its Treatment with Lyovac Antitularemic Serum is described in a case reported by G Edward Marr[4]

Man, 25 became ill on November 24, complaining of sore throat, headache and general malaise anorexia and nausea chills and fever and dull pain in the lower left side of the chest with a dry nonproductive cough On physical examination he appeared acutely ill and prostrated Temperature was 101 8 F pulse rate 106 and respirations 22 His tongue was coated, breath foul and pharynx injected Respirations were costo abdominal in character with bronchial breathing *scattered piping and submucous rales and isolated areas of* dulness to percussion throughout the left side of the chest particularly over the left base posteriorly The skin was hot dry and flushed Diagnosis was acute bronchitis with mild bronchopneumonia The patient was placed on the regimen indicated and was not heard from until a week later In the interim he had begun to expectorate a moderate amount of thick yellowish phlegm and there had developed a match head sized pustule on the dorsum of his second right finger with barely palpable nontender right axillary glands Physical findings were otherwise unchanged At this time a history of having skinned and cleaned rabbits a week prior to onset of the present illness was elicited

The patient was hospitalized on December 1 Laboratory findings on admission were blood pressure, 116/60 urine negative hemoglobin 84 per cent red blood cells 4,270,000 white blood cells, 10 200 polymorphonuclears 83 per cent lymphocytes, 17 per cent Sputum was negative for tuberculosis and pneumococci An intracutaneous tularemia test with Fosbay vaccine was strongly positive Kline and Kahn tests were negative

(4) Ohio St te M J 3 1154 1155 December 1941

tient was uncooperative and incoherent There was a small ulcer about 3 mm in diameter on the dorsum of the right index finger The right axillary lymph nodes were enlarged tender and painful An agglutination test for tularemia on January 2 showed a few clumps in a 1 20 dilution On January 7 the test was positive at 1 320

Until January 3 he was treated symptomatically Sulfathiazole and neoar phenamine were next used On January 11, he was given 100 mg acriflavine dissolved in 250 cc physiologic saline solution intravenously This was followed by 1 000 cc of 5 per cent glucose in physiologic saline as an infusion That afternoon the patient said he felt fine The temperature for the first time failed to exceed 100 F The next day there was marked clinical improvement Pain had disappeared The enlarged and painful right axillary lymph nodes suddenly seemed to become painless Maximum temperature on January 12 was 99 6 F On January 14 another 100 mg acriflavine was given The next morning the temperature was 98 F and thenceforth remained normal Return of strength was rapid and the patient was discharged on January 19

On February 11 he felt strong and completely recovered He had gained about 10 lb The enlarged axillary lymph nodes were still painless and seemed to be regressing The region of the primary lesion showed a darkly pigmented small scar

Case 2—Man 21 who had been cleaning rabbits in large numbers began experiencing chills and general malaise on November 26 He was treated for influenza On November 29 he first noted a small painless mass in his left axilla and on November 30 he was hospitalized Examination revealed a small lesion that had been present for several days on the dorsal aspect of the left middle finger A diagnosis of ulceroglandular tularemia was made The agglutination test for tularemia was positive He was treated with large doses of sulfathiazole and discharged December 29

Typhoid in Large Cities of the United States in 1940[7] The number of cities with no death from typhoid has increased to 41 In 1936 there were but 18 such cities in 1937 27 in 1938 29 and in 1939 34 In 1939 there were 14 cities with no typhoid death for at least two years in 1940 there were 18 such cities The cities are grouped in rank in the table In 1938 and again in 1939 there were three cities in third rank (rate in excess of 5) however in 1940 no city fell in this rank Less impressive is the fact that in 1940 there were 12 cities with rates in excess of 2 while there were but 10 such cities in 1939 In Trenton all deaths were among nonresidents and in six of the remaining cities with rates in excess of 2 the records indicate that one third or more of deaths were among nonresidents Nine cities in the first rank (Boston Columbus Akron Oakland Atlanta Salt Lake City Albany Evansville and Syracuse) would appear (in addition to Trenton) in the honor roll were they not charged with deaths in nonresidents

For the quinquennium 1936-1940 the cities of the New England states have the lowest rate (0 39) followed in

DEATH RATES FROM TYPHOID IN 1940

Honor Roll No Typhoid Deaths (41 Cities)¶

Buffalo	Lowell	South Bend
Cambridge	*Lynn*	*Spokane*
Camden	Milwaukee	Springfield
Canton	Newark	St Paul
Charlotte	New Bedford	*Tampa*
Denver	New Haven	Tulsa
Des Moines	Peoria	Utica
Duluth	Portland	*Waterbury*
Erie	Reading	Wichita
Fall River	Rochester	Wilmington
Fort Wayne	Sacramento	Worcester
Grand Rapids	San Diego	Yonkers
Hartford	Scranton	Youngstown
Jacksonville	Seattle	

¶ Th ty m e w th t Ch I tt d S c me o

(7) J A M A 118 2 6 J n 17 1942

moderate clinical improvement, the patient continued to run a low grade fever on April 7 examination showed a moderately enlarged liver and palpable spleen The axillary sinus was still draining slightly Roentgen therapy to the spleen caused it to diminish in size, epigastric discomfort disappeared

Despite apparent improvement following roentgen therapy, the patient continued to be febrile and by April 14 the fever began going over 100 F Rest in bed and symptomatic treatment caused no improvement and the patient was again hospitalized April 28 Another agglutination test for tularemia was reported positive The patient was given eight intravenous administrations of acriflavine according to the usual method (April 29 and 30 May 1, 3 5 7 10 and 14) After the second treatment he felt much better his strength seemed to return, appetite improved and he was able to rest better Each acriflavine injection was followed by a slight temperature rise of not more than 1 degree with the exception of the last, when temperature did not exceed normal Clinical improvement was marked and the patient was discharged May 18

Loria believes that the acriflavine acted as a bacteriostat inhibiting the growth of the organisms sufficiently to permit the host enough time to increase his antibodies to the point of finally overcoming the infection In each case it appears that the body defense did not become definitely well established until acriflavine was administered In Case 2 the drug eventually had to be given more frequently in order to have a definite inhibitory influence on the growth of the offending organism

administered orally in orange juice thrice weekly until 40 doses had been given The patients were kept on a low fat diet to avoid unnecessary gallbladder contractions For the same reason the dye was given early in the morning so that maximum dye concentration in the gallbladder was reached at night when rest and absence of food intake might permit the gallbladder to remain quiescent

Sterilization of bile was obtained in 21 (32 3 per cent) of the 65 carriers thus treated but 16 of these 21 continued to excrete typhoid bacilli in the stools indicating an additional intestinal carrier state

Five intestinal carriers whose bile was free from typhoid bacilli as the result of iodophthalein treatment or because of the finding of bacilli in the feces in the presence of negative bile were treated with sulfaguanidine 0 05 Gm per Kg four times daily for two weeks In all bacillary excretion continued unabated

Although bile sterilization with iodophthalein as reported here has not resulted in the high percentage (75) of cures reported in series of similar patients treated by cholecystectomy the authors believe that such conservative treatment should be considered before cholecystectomy is resorted to particularly in bile carriers past 50 and in the presence of a well functioning gallbladder as determined by cholecystogram The safety of conservative treatment as compared with the mortality of cholecystectomy and the possible improvement of results with changes in dosage and duration of treatment favor such conservatism

[Iodophthalein treatment would certainly seem indicated before resorting to surgery —Ed]

First Rank From 0 1 to 1 9 Deaths per 100 000 (43 Cities)§

City	Rate	City	Rate	City	Rate
Boston	0 1*	Long Beach	0 6	Gary	0 9
Chicago	0 1	Philadelphia	0 6	Tacoma	0 9
New York	0 1	Washington	0 6	Evansville	1 0
Columbus	0 3*	Atlanta	0 7	Syracuse	1 0
Baltimore	0 3†	Salt Lake City	0 7	Indianapolis	1 0
San Francisco	0 3†	Cincinnati	0 7†	Oklahoma City	1 0
Detroit	0 3	Jersey City	0 7†	Fort Worth	1 1
Akron	0 4	Kansas City Mo	0 7†	Miami	1 2
Los Angeles	0 4†	Cleveland	0 7	Providence	1 2
St. Louis	0 4†	Flint	0 7	Chattanooga	1 6
Minneapolis	0 4	Paterson	0 7	Houston	1 6
Omaha	0 4	Albany	0 8	Kansas City Kan	1 6
Pittsburgh	0 4	Louisville	0 9†	Memphis	1 7†
Toledo	0 4	Elizabeth	0 9	Knoxville	1 8
Oakland	0 6*				

Second Rank From 2 to 4 9 (12 Cities)

City	Rate	City	Rate	City	Rate
Bridgeport	2 0	Richmond	2 6	Dallas	3 0†
Somerville	2 0	San Antonio	2 7	El Paso	3 1†
Trenton	2 4	Norfolk	2 8†	Birmingham	3 4†
New Orleans	2 4†	Dayton	2 8	Nashville	3 6†

§ Forty two without Gary

All typhoid deaths were stated to be in nonresidents

† One third or more of the reported typhoid deaths were stated to be in nonresidents

order by the Middle Atlantic (0 43) and East North Central groups (0 53) The West North Central and Mountain and Pacific groups have the same rate (0 60) For the 78 cities for which data are available since 1910 there occurred 172 deaths from typhoid in 1940 which is the lowest on record (257 in 1938 232 in 1939) The rate for all cities is now about 0 50 per 100 000 population No outbreaks have been recorded Preventive measures have been the same as reported for previous years

The Typhoid Carrier Problem Studies on 110 fecal typhoid carriers are reported by William Saphir Walter H Baer and Frederic Plotke[8] (Manteno Ill State Hosp) Ninety five were submitted to biliary drainage and 65 were found to be bile carriers These bile carriers were subjected to biliary antiseptic treatment with soluble iodophthalein Four Gm soluble iodophthalein was

(8) J A M A 118 964 967 Mar 1 1942

administered orally in orange juice thrice weekly until 40 doses had been given The patients were kept on a low fat diet to avoid unnecessary gallbladder contractions For the same reason the dye was given early in the morning so that maximum dye concentration in the gallbladder was reached at night when rest and absence of food intake might permit the gallbladder to remain quiescent

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[Iodophthalein treatment would certainly seem ind cat d before e orting to surgery —Ed]

cumbersome for large scale production The two remaining vaccines those of Castaneda and of Cox can be produced in quantity and from available results on animals give promise of producing immunity in man Experimentally Castaneda s vaccine has been shown to protect man against subsequent inoculation with infectious material The final answer on both vaccines awaits their use under controlled conditions in the presence of typhus epidemic Neither of these vaccines has been tried out adequately under such conditions although vaccine prepared by the Cox method is on trial in various countries where there is danger of epidemic typhus—Romania Hungary Spain and China

Vaccination against Typhus Fever Cholera and Plague Methods are described in Circular Letter no 3 issued by the Office of the Surgeon General U S Army Washington D C

Typhus Fever—The approved vaccine consists of a suspension of killed louse borne epidemic typhus rickettsiae prepared by the Cox yolk sac cultured method Initial vaccination consists of three 1 cc injections administered subcutaneously at 7 to 10 day intervals A stimulating dose of 1 cc may be administered every four to six months as long as serious danger of infection exists

Cholera—The approved vaccine consists of a suspension of 8 000 million of killed cholera vibrios per cc Initial vaccination consists of two subcutaneous injections the first 0 5 cc and the second 1 cc administered with a 7 10 day interval between injections A stimulating dose of 1 cc may be administered every four to six months as long as serious danger of infection is present

Plague—The vaccine consists of a suspension of 2 000 million killed plague bacilli per cc Initial vaccination is the same as that for cholera Additional 1 cc doses may be administered when deemed necessary

(2) W M d 139 141 J u ry 194

It is imperative to realize that vaccination alone is not adequate for the prevention of typhus cholera or plague The immunity conferred is incomplete and probably of short duration Vaccination should therefore be considered an adjunct to other control measures

Control of Rickettsias by immunization against infection is discussed by G W M Findlay [3] To be of value against human rickettsial infection a vaccine must produce a high degree of lasting immunity be devoid of dangerous reactions and be easily produced and administered. Few such vaccines comply with these requisites Vaccines however have been prepared against exanthematic and murine typhus Rocky Mountain spotted fever and more recently Q fever Two methods of inoculation have been suggested for immunization against exanthematic typhus

The first is based on the fact that the rickettsia of murine typhus is closely related to that of exanthematic typhus and that the former produces a much milder disease than the latter Accordingly experiments have been made on the effect of injecting murine typhus rickettsias into man Egg yolk mouse brain vaccine and bile treated vaccine have been used Both have been proved disadvantageous in that severe reactions follow their use in nonimmune persons

Killed exanthematic typhus vaccine has also been used but an associated difficulty lies in obtaining dead rickettsia in sufficient numbers Good results have been obtained however in the relatively small series in which such vaccine has been used The problem of vaccine supply may shortly be solved by use of the developing chick embryo and the fact that a variety of rickettsias can be adapted to mouse lung

Endemic (Murine) Typhus Fever George W Stober [5] (Cleveland) tabulates some of the differentiating clinical and epidemiologic features of endemic (murine)

(3) L n t 1 483-484 Ap 18 194
(5) Oh bt te M J 3 644 645 J ly 1941

typhus fever and Rocky Mountain spotted fever Such differentiation has assumed importance since both diseases have been reported in Ohio

Rocky Mountain Spotted Fever	Endemic Typhus Fever
1 Sudden onset with chills headache and rising temperature	1 Same except splitting headache and insomnia may be outstanding
2 Daily temperature fluctuations often reaching 105 F continues 15–22 days or until death	2 Similar temperature range terminates by crisis in 12–14 days
3 Macular rash on wrist and ankles 3–5 days after onset later becomes generalized occurring on palms soles and face macules 2–6 mm in diameter are faint rose at first and petechial by the second week many become confluent and some papular rash persists several weeks desquamation follows	3 Macular rash 4–6 days after onset confined to chest abdomen back and medial surfaces of the extremity may become generalized but never appears on face and rarely on soles and palms macules 2–3 mm rose to dark red do not become petechial many are papular rash continues 2–9 days no desquamation.
4 Delirium common hyperesthesia and tremors noted	4 Delirium less common hyperesthesia and tremors rare
5 Agglutination with proteus X19 but absent in many cases agglutinins appear the second week or later agglutination occurs in some cases in high dilutions of over 1 10 000	5 Agglutination with proteus X19 almost always present in high dilutions agglutinins appear the second week or later
6 Occurrence in spring summer and fall	6 Common in summer and fall
7 More common in white race in males and children	7 More common in white race in males and adults
8 Animals including rodents may act as reservoirs but what animals has not been proved	8 Rat is the animal reservoir
9 Vectors are Dermacentor variabilis in the east and Dermacentor andersoni in the west	9 Rat flea Xenopsylla cheopis is common insect vector
10 Transmission through bites of infected ticks	10 Transmission by infected fleas
11 Incubation period 4–12 days	11 Incubation period 14 days
12 Disease of rural areas	12 Urban disease
13 Case fatality rate 15–70 per cent 25 per cent being average rate	13 Fatality rate less than 1 per cent

The Diagnosis of Exanthematous Typhus of Brazil in Minas Geraes, according to Octavio de Magalhães[4] is dependent on (1) the clinical aspect of certain serious cases of slow evolution and (2) isolation of the virus in guinea pigs or rhesus monkeys by intraperitoneal inoculation of blood Isolation of the virus is the most definite and infallible diagnostic procedure Clinical aspects of the disease lend diagnostic certainty only in some of the serious cases for the disease may be so manifest as to be confused with other contagious diseases

Of the fundamental symptomatic triad exanthems, fever and nervous phenomena the exanthem alone is diagnostic It is the most distinctive of the clinical symptoms Other symptoms which aid in diagnosis are icterus facial edema splenomegaly hepatomegaly myalgia cardiac circulatory and pleuropulmonary disorders, albuminuria with casts chloride retention azotemia and acidosis Without the exanthem however clinical diagnosis is always uncertain

The Weil Felix reaction is of diagnostic value but not in the early stages a high percentage of negative results being obtained in the first five days of the disease

Pathology of Rocky Mountain Spotted Fever R D Lillie[6] states that there is no essential difference between the lesions of Rocky Mountain spotted fever in the Rocky Mountain area and those in the eastern seaboard of the United States The fundamental lesion is vascular It is characterized by endothelial swelling and proliferation perhaps with rickettsiae in endothelial and perithelial cells sometimes going on to vascular occlusion or to endothelial necrosis or hyaline or karyorrhectic cellular thrombosis or both necrosis and thrombosis cellular infiltration and necrosis of the walls of precapillary vessels particularly arterioles There is often associated an independent perivascular cellular infiltration comprised of polymorphonuclear leukocytes (chiefly

(4) J Trop Med & Hyg 44 134 1 9 Oct 15 1941
(6) Nat Inst of Health Bull n 177 pp 1 59 1941

in the presence of vascular necrosis) predominantly lymphocytes and in later stages larger lymphoid and plasma cells and monocytes These lesions are considerably modified by anatomic location and not all phases are encountered in every organ in which lesions occur The occurrence of rickettsiae in round cells outside vessels is still dubious as considerable difficulty has been encountered at times in deciding whether an individual cell laden with small basophilic granules is a tissue mast cell or a lymphoid or monocytoid cell laden with purely coccoid rickettsiae Mast cell granules generally exhibit distinct metachromasia and clusters of rickettsiae will usually show a few bacillary forms on close examination

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VIRUS DISEASES

Neurotropic Virus Diseases of Man are reviewed by Albert B Sabin[7] (Univ of Cincinnati) These are divided into epidemic and nonepidemic groups (Table 1) Of these with the exception of the viruses of polio

TABLE 1 —Neurotropic Virus Diseases of Man

Epidemic	Nonepidemic
Poliomyelitis	Lymphocytic choriomeningitis
Encephalitis	Pseudolymphocytic choriomeningitis
Lethargica (Economo s)	Western equine encephalitis
St Louis	Rabies
Japanese type B	Louping ill
Eastern equine	B virus disease
Australian X	Herpes simplex
	Herpes zoster
	Acute nonsuppurative encephalitis (unknown etiology)

Postinfection encephalitis measles varicella vaccinia mumps etc

myelitis rabies and herpes simplex all have been isolated recognized and identified Aside from the fact that the 11 viruses known to affect the human nervous system are all immunologically distinct identification can usually be accomplished by determining whether

(7) J Pd t 19 44 4 1 Ot 1941

TABLE 2—SOME PROPERTIES OF VIRUSES AFFECTING THE HUMAN NERVOUS SYSTEM

Virus	Pathogenicity or Usual Laboratory Animals				Size $m\mu$	Inclusions
	Rhe[illegible] M[illegible]keys	Mice	G[illegible] P[illegible]g	R[illegible]bb[illegible]ts		
Poliomyelitis	+	0	0	0	10	Intranuclear type B
Encephalitis (St Louis)	0 to ±	+	0	0	25	0
(Japanese)	+	+	0	0	Small	0
Louping ill	+	+	0	0	17	0
[illegible]ymphocytic choriomeningitis	+	+	+	0	50	0
Pse[illegible]ymphocytic choriomeningitis	+	+	0 or ±	0	185	0
Equine e[illegible] (eastern) [illegible]halitis	+	+	+	+	25	Intranuclear type B
(western)	+	+	+	+	25	Intranuclear type B
Rabies	+	+	+	+	12[illegible]	Cytoplasmic Negri bodies
B virus	+	0 to ±	0 to ±	+	125	Intranuclear type A
Herpes simplex	0	+	+	+	125	Intranuclear type A

[illegible]

or not the unknown virus can produce disease in rhesus *monkeys mice guinea pigs and rabbits* by *estimating* its approximate size from its capacity to pass certain filters and by the type of change it produces in infected cells These properties are summarized in Table 2 The determination of the pathogenicity of a virus for a given number of animals is used in the same manner and is as helpful for purposes of identification as is the determination of the types of culture mediums on which unknown bacteria will grow

Complement Fixation Test in Diagnosis of Virus Infections of the Central Nervous System J Casals and R Palacios[8] (Rockefeller Inst) report that a specific complement fixation test can be obtained in various virus infections of the central nervous system by using as antigens emulsions of infected brain tissue freezing and thawing the brain emulsion and then centrifuging it in an angle head centrifuge at 3 500 r p m. for one hour The method has proved reliable in the case of rabies St Louis encephalitis Japanese B encephalitis lymphocytic choriomeningitis Eastern equine encephalomyelitis Western equine encephalomyelitis louping ill and spontaneous encephalomyelitis of mice (Theiler s disease)

The specificity of the reaction regardless of the virus involved requires different temperatures of inactivation of the serums according to animal species 56 C for guinea pig 60 C for mouse and 65 C for rabbit and dog serums all heated for 20 minutes For human serums a temperature of inactivation of 60 C also for 20 minutes has been adopted at this temperature the reaction is in general specific

Complement fixing antibodies in high titer were found in the serums of rabbits guinea pigs mice and dogs immunized with rabies virus Complement fixing antibodies were present in high titer in serums drawn from two persons 8 years after an attack of louping ill from

(8) J E p M d 74 409 4 6 N 1 1941

five persons 2½ years after an attack of Eastern equine encephalomyelitis and from two persons 2½ years after an attack of Western equine encephalomyelitis In cases of St Louis encephalitis and lymphocytic choriomeningitis complement fixing antibodies have been found shortly after infection but not after long periods

Clinical Observations on Sandfly Fever in the Peshawar District W M E Anderson[9] describes sandfly fever as an acute fever of short duration and no mortality caused by a specific virus transmitted by the bites of the sandfly Phlebotomus papatasii The disease occurs in tropical and subtropical countries notably the Mediterranean area Northern India and parts of America under various names e g, Papatasii fever, three day fever Mediterranean dengue summer influenza In the North west Frontier Province (India) and to a lesser extent in the Punjab sandfly fever presents a significant military problem because of its almost *epidemic proportion each year* There is no generally available specific laboratory test for this disease and diagnosis which may be difficult can be reached only through clinical observation

Both severe and mild cases occur the difference seemingly being dependent on individual resistance Clinical features of the severe type include a fever of acute onset lasting two to five days and characterized by frontal and supra orbital headache retro ocular pain photophobia backache myalgia chiefly in the legs and often in the orbital muscles flushing of the face conjunctival suffusion often most marked toward the canthi coating of the tongue usually with a red margin faucial injection, leukopenia and relative bradycardia Some of these features are usually absent in mild cases but there is usually sufficient evidence for diagnosis

Treatment consists of keeping the bowels open rest in bed liberal fluids and no solid food Diaphoretics such as aspirin or salicylates are given four hourly

(9) J R y Army M C rp 77 5 39 November 1941

until temperature subsides Patients with severe head ache may require opium The effectiveness of sulfon amides has not been evaluated

Treatment of Yellow Fever is discussed by Fred L Soper[1] (Rio de Janeiro) Yellow fever shows marked variability in severity and uncertainty in prognosis Once established there are no specific serologic or chemo therapeutic agents of value It constantly produces a high grade and permanent immunity in man but im mune serum therapy is ineffective because onset of symptoms apparently occurs only after the virus has been safely entrenched in the cells throughout the body in which position immune serum is powerless to inac tivate or prevent development of the virus

Immune serum was extensively used for protection of laboratory workers until development of vaccination with modified strains Such passive immunization how ever is fleeting and uncertain and should not be relied on for more than a few days following inoculation The virus strain now used known as 17 D is largely without viscerotropic affinity for liver and kidney and in con trast to the strain previously used shows greatly re duced neurotropism It grows readily in chick embryo and the infected embryo itself is used in vaccine prep aration Only one inoculation is given Successful vaccination depends on delivering living virus under the skin of the person being vaccinated Inactivated virus is not antigenic and every precaution should be taken to protect vaccine virus against moisture heat sunlight and other harmful agents Reactions to virus 17 D are rare and consist only of slight headache and malaise for some hours five to eight days after inocula tion Active immunity thus produced has persisted un altered during the four year period since field use of this vaccine began

Despite lack of specific treatment careful handling of all patients even those with mild involvement is in

(1) J A M A 118 374 378 J 31 194

dicated Involvement of the circulatory system occurs early, is often severe and may persist far into con valescence therefore the patient should from the begin ning have absolute bed rest in a recumbent position He should not be moved from the place of attack, espe cially after the first day Resumption of activity should be gradual Careful nursing is essential

The gastro intestinal tract should be relieved of its routine responsibilities An initial saline purge may be given the first day followed by daily enemas Only fruit juices to combat hypoglycemia should be allowed during the phase of infection and until after the tem perature has returned to normal in the phase of in toxication Water, Vichy water or water alkalized with sodium bicarbonate and citrus fruit juices may be given frequently in small amounts If vomiting pre vents taking liquids by mouth intravenous dextrose, physiologic solution of sodium chloride by hypodermoc lysis and tap water by rectum may be tried For direct relief of vomiting cracked ice and 0 015 Gm cocaine hydrochloride U S P may be given by mouth and 0 03 Gm codeine sulfate U S P by hypodermic Feeding should be resumed slowly beginning with chicken broth buttermilk rice water crumbled egg yolk and easily digested liquids with added lactose

A high temperature may be relieved by an ice cap to the head and tepid sponge baths Depressant anti pyretic drugs should not be used

Results of blood analysis seem to indicate use of dextrose to combat hypoglycemia and of calcium salts to neutralize the guanidine like toxins common in condi tions causing destruction of the liver parenchyma use of calcium lactate and dextrose has had no striking re sults in man

Cuba and Yellow Fever W H Hoffmann (Habana) reviews the advances made in study of yellow fever and in the campaign against it since Finlay discovered

( ) Rev d med y ci Hab a 46 399-420 Sept 30 1941

its vector Aedes aegypti Cuba has been free from the disease for 40 years and under normal conditions would have no more epidemics But histologic investigations at Finlay Institute have revealed that all countries of Africa and South America in which there were epidemics previously are still endemic centers which cannot be sanitated by present methods The danger of importation of the infection into Cuba increases with the rapidity and frequency of communications and as the number of immune persons decreases annually and Aedes aegypti is common in the island conditions are favorable for epidemic propagation

In doubtful or suspicious cases the physician must always consider the possibility of yellow fever until the case is proved harmless he must treat any suspicious case as yellow fever isolate the patient and kill the mosquitoes found in the house He must make a careful clinical observation including the history and symptoms especially the presence and course of albuminuria and hemorrhages the pulse and temperature which must be charted every two hours In case of death an autopsy must be made to discover indications of another cause if the suspicion or possibility of yellow fever persists a small specimen of the liver kept in 10 per cent formaldehyde must be sent to Finlay Institute for histologic examination If complete autopsy is impossible the liver specimen can be taken through a small incision

In case of yellow fever the mosquitoes in the house in which the patient was while infectious are killed and all persons exposed to the infection are vaccinated Vaccine can be obtained in a few hours from the Public Health Department of Miami Lay collaboration against the threatening danger is sought in the local press The public health authorities look out for secondary cases incubation of the virus in the mosquito takes 12 days before it can be transmitted so that these cases may be expected from 14 to 20 days after the first case and will suggest an epidemic infection or real danger of

an epidemic The 1928 epidemic of Rio de Janeiro lasted several months and killed about 200 persons showing that the danger presented by an epidemic is still rather serious but can be overcome by the usual sanitary measures

Persistent Myalgia Following Sore Throat is reported by L E Houghton and E Idris Jones[3] Seven hospital nurses developed streptococcic sore throat followed in 8 to 21 days in six of them by myalgia Usually muscle pains appeared first in the left side of the chest then in the calves of the legs thighs arms and neck Pain was aggravated on movement was worse at night and was sufficiently severe to withstand the action of common analgesics Pain was of three types dull and boring sharp and localized or shooting running the length of a muscle to the toes or fingers Chest pains disappeared after a few days but the limb pains sometimes persisted for months Associated with the myalgia was an evening temperature rise to 100 101 F this rise persisting for three weeks to five months in different cases Frequently a definite hardening was palpable over the painful area and pressure on this area produced acute pain The overlying skin was never reddened or indurated Associated features were severe headache with neck rigidity in one case waves of depression and menstrual disturbances Epistaxis was common and subungual hemorrhages occurred in two cases

All investigations including skin tests and precipitin reactions for trichinosis were negative Biopsy of a painful indurated area in a muscle showed no abnormalities and no treatment was found to be of any value All patients recovered without sequelae It is suggested that the condition is due to an unidentified myotropic strain of virus

[It is difficult to understand the lack of abnormal findings in biopsy specimens in one case described since the areas of induration would indicate the presence of —Ed]

(3) Lancet 1 196 198 Feb 14 1

WHOOPING COUGH

Pertussis Prophylaxis with Two Doses of Alum Precipitated Vaccine Joseph A Bell[4] (Nat l Inst of Health) reports that two 1 cc doses of alum precipitated pertussis vaccine injected with a four week interval between doses into a large proportion of a group of children in Norfolk Va conferred real protection against clinical attacks of the disease Each cubic centimeter represented a saline suspension of 10 billion unwashed pertussis bacilli and their products killed with 0 5 per cent phenol and precipitated by the addition of 0 027 cc of 10 per cent sodium bicarbonate solution and 0 25 cc of 4 per cent potassium alum solution *after washing the precipitate once in 0 85 per cent* saline it was suspended in 1 cc of 0 85 per cent sodium chloride solution containing 1 7 500 merthiolate One cc was injected subcutaneously into the deltoid region of one arm of very young children and after a four week interval a similar dose was injected into the other arm The total amount of vaccine here injected represented only 20 billion organisms whereas 80 120 billion organisms have been commonly recommended for prophylactic pertussis immunizations

The table presents the total white and Negro experience with pertussis during the 34 month observation period The Negro V group was more completely vaccinated than the white V group and the Negro N group more completely not vaccinated than the white N group Ninety eight per cent of the children in the Negro V group received one or more injections of pertussis vaccine prophylactically as against 91 per cent in the white V group and 91 per cent in the Negro N group were entirely without prophylactic vaccine as against 85 per cent in the white N group

It is believed that the observed incidence of pertussis

(4) P b H lth Rep 56 1535 1546 A g 1 1941

in the N group is normal because nothing was done to this group which would be expected to influence appreciably the incidence and because the estimated average annual attack rate (110 per 1,000) for the white children observed approximates that commonly reported for white children in this age group and environment, even though the observed experience covers one and a half epidemic periods and only one interepidemic period

DISTRIBUTION OF DEFINITE CASES OF PERTUSSIS OCCURRING DURING 34 MONTHS IN WHITE AND NEGRO CHILDREN ACCORDING TO SELECTION IN V OR N GROUP

COLOR	SELECTION	NO OF CHILDREN	NO OF CASES	PER CENT ATTACKED	RATIO N PER CENT/V PER CENT
White	V	220	26	11 82	
	N	199	62	31 16	
	Total	419	88	21 00	2 64
Negro	V	273	25	9 16	
	N	233	88	37 77	
	Total	506	113	22 33	4 12
White and Negro	V	493	51	10 34	
	N	432	150	34 72	
	Total	925	201	21 73	3 36

Since the V and N groups were strict random samples of the combined groups since the observation of each group was pursued with equal diligence and uniform criteria were used to enumerate cases and since the only known difference between the groups was the injection of alum precipitated pertussis vaccine into a large proportion of the V group of children whereas only a small proportion of the N group were so injected it is believed that the vaccine used was responsible for the disproportionately smaller number of cases of pertussis observed in the V as compared with the N group or with the combined groups

Treatment of Whooping Cough Bronchopneumonia William P Frank Edwin F Patton and Paul M Hamilton[5] (Los Angeles County Hosp) evaluate results achieved with hyperimmune pertussis serum sulfapyridine and sulfathiazole Thirty consecutive patients with whooping cough bronchopneumonia were treated with large doses of hyperimmune pertussis serum with a mortality rate of 20 per cent In only nine cases did the temperature become normal within 24 72 hours Sixteen patients were treated with sulfapyridine with a mortality rate of 25 per cent Only four responded to the drug within four days

Seventy seven consecutive patients were treated with sulfathiazole with a mortality rate of 4 per cent Among these were 32 patients under 1 year of age and 2 died 24 patients aged 1 2 years and 1 died and 21 patients aged 2 7 years and none died Improvement did not come by crisis but by lysis the temperature on the average returning to normal in four days The blood concentration of sulfathiazole needed for good results was relatively low about 2 3 mg per cent

Important therapeutic adjuncts were special nurses during critical periods hand feeding of babies sedatives as indicated diets fortified with large amounts of vitamins A B C and D oxygen and parenteral fluids as indicated.

(5) J Ped t 0 7 0 7 2 Ju 194

Chemotherapy in Infectious Diseases and Other Infections is described in Circular Letter no 17 issued Feb 23 1942 by the Office of the Surgeon General of the United States Army [6] Therapy in the following conditions is discussed hemolytic streptococcic infections scarlet fever meningococcic and purulent meningitis pneumonia gas bacillus infections staphylococcic infections peritonitis and urinary tract infections

1 Hemolytic streptococcic infections (*a*) Mild or moderately severe hemolytic streptococcic infections such as erysipelas mild cellulitis and tonsillitis For specific treatment sulfadiazine is the drug of choice Initial dose is 4 Gm orally followed by 1 Gm every four hours day and night until five days of normal temperature have elapsed A blood concentration of 5 to 10 mg per cent sulfadiazine is desirable

b) Otitis media This is generally caused by hemolytic streptococci but may be caused by pneumococci or other organisms and presents a special case Treatment should be started as outlined in (*a*) above Cultures should be taken Therapy should be continued in 0 5 Gm doses four times daily for at least 10 days after clinical cure

c) Severe hemolytic streptococcic infections such as meningitis septicemia severe cellulitis acute osteomyelitis acute mastoiditis Sulfadiazine should be given as in (*a*) above and continued until temperature has been normal for seven days If sulfadiazine is not available sulfanilamide should be used in the same dosage In acute streptococcic mastoiditis or osteomyelitis sulfadiazine should be continued in 0 5 Gm doses four times daily for at least 10 days after clinical cure In severe infections sodium sulfadiazine may be used intravenously Initial dose by this route is 0 10 Gm per Kg

(6) W Med 46:491 M y 194

following which it is generally sufficient to continue therapy with 1 Gm sulfadiazine orally every four hours day and night until temperature has been normal for seven days If therapy is continued intravenously subsequent doses of 0 05 Gm per kg should be administered at 12 hour intervals It is always advisable to shift to oral administration of sulfadiazine as soon as possible

A blood concentration of 15 mg per cent sulfadiazine should be maintained during the febrile phase of serious hemolytic streptococcic infections

2 Scarlet fever During the exanthematous stage of simple toxic scarlet fever globulin concentrated antitoxin should be given in one dose 18 000 units intramuscularly in moderately severe cases 27 000 36 000 units intravenously in severe cases and 45 000 units intravenously in very severe cases Sulfadiazine has no therapeutic effect on the toxic stage but should be used for prophylaxis of septic complications in 0 5 Gm doses four times daily during the period of quarantine

During the exanthem of toxic and septic scarlet fever i e cases with complicating early septic lesions such as purulent rhinopharyngitis sinusitis otitis media mastoiditis and marked lymphadenitis antitoxin should be given as above but in larger dosage moderately severe 27 000 units severe 45 000 units very severe 63 000 units Sulfadiazine should be given for chemotherapeutic effect on septic lesions with initial dose 4 Gm orally followed by 1 Gm every four hours until temperature has been normal for five days then 0 5 Gm four times daily for the period of quarantine Sulfanilamide should be used if sulfadiazine is not available

For late postexanthematous septic complications sulfadiazine should be given as outlined for septic complications

3 Meningococcic meningitis Antimeningococcic serum is not recommended unless deemed necessary in the individual case Sulfadiazine is the drug of choice Initial dose is 4 Gm orally followed by 1 Gm every four

hours until temperature has been normal for seven days Sulfanilamide in similar dosage may be used in absence of sulfadiazine Sodium sulfadiazine may be given intravenously as outlined under 1 *c* Lumbar puncture is indicated only for diagnosis and subsequently only to relieve symptoms of increased intracranial pressure

4 Other forms of purulent meningitis (pneumococcic staphylococcic and cases of unknown etiology) Sulfadiazine therapy should be instituted at once with initial dose (oral) 4 Gm and 1 Gm every four hours day and night If response is not satisfactory increase to 1 5 to 2 Gm every four hours until improvement is definite then reduce dose to 1 Gm every four hours and continue until temperature has been normal for seven days If oral treatment is impossible sodium sulfadiazine should be given intravenously as outlined under 1 *c* If sulfadiazine is not available or response is not satisfactory sulfathiazole or sodium sulfathiazole should be substituted in the same dosage

5 Pneumonia In primary pneumonia sulfadiazine should be started immediately in initial dose of 4 Gm followed by 1 Gm every 4 hours until 72 hours of normal temperature have elapsed and a concomitant improvement in the patient s condition has occurred In severe cases or in patients unable to take oral medication sodium sulfadiazine may be given intravenously as outlined under 1 c A blood concentration of 8 to 12 mg per cent sulfadiazine is desirable during the febrile phase Fluids should be forced to 3 500 cc per day

Homologous type antipneumococcus serum preferably rabbit serum is recommended in addition to sulfadiazine therapy in early cases *(less than 72 hours after onset)* only when the patient fails to show satisfactory response to 48 hours of chemotherapy which occurs rarely or in late cases (over 72 hours after onset) which clinically appear unusually severe and are presumptively bacteremic or when the patient fails to respond to chemotherapy alone In early cases an initial dose of 200 000

units of homologous antipneumococcic rabbit serum is given intravenously In late severe presumptively bacteremic cases initial dosage is 300 000 units If these doses prove insufficient subsequent doses of 100 000 units each should be given every eight hours

In hemolytic streptococcic pneumonia and Friedlander s bacillus pneumonia sulfadiazine should be given as above If response is not satisfactory increase to 1 5 to 2 Gm every four hours until improvement is definite then reduce dose to 1 Gm every four hours and continue until temperature has been normal for five days If sulfadiazine is not available sulfathiazole may be used orally in the same dosage

In staphylococcic pneumonia sulfathiazole or sulfadiazine may be given orally as outlined for streptococcic pneumonia Sodium sulfathiazole may be used with initial dose 4 Gm and subsequent doses 2 Gm every six hours Sodium sulfathiazole is given intravenously as a 5 per cent solution It is advisable to change to oral dosage as soon as possible

In secondary pneumonia sulfadiazine is recommended in all cases in which pneumococci hemolytic streptococci or Friedlander s bacilli are found and believed to be of etiologic significance If staphylococci predominate sulfathiazole or sulfadiazine may be used Administration is the same as in primary pneumonias

Chemotherapy with sulfonamide derivatives is of no demonstrable value in many bronchopneumonias of indeterminate (virus?) etiology and streptococcus viridans or Haemophilus influenza pulmonary infections Results in secondary pneumonias which are often mixed infections are therefore variable often disappointing and difficult to evaluate even when bacteria known to be susceptible to the sulfonamide compounds are present in the sputum

6 Gas bacillus infections In serious injuries in which gas bacillus infection is likely all rational surgical procedures such as debridement should be carried out as

soon as possible Sulfanilamide is the drug of choice for prophylaxis Initial dose is 6 Gm orally, followed by 1 Gm every four hours for seven days This usually eliminates the possibility of gas bacillus infection Crystalline sulfanilamide should be distributed evenly over the surface of the wound using approximately 0 1 Gm per sq in but not over 10 Gm for any one person Polyvalent gas gangrene antitoxin 11 000 units should be used when deemed necessary

For treatment of gas bacillus infections sulfathiazole is the drug of choice Initial dose is 6 Gm orally, followed by 1 Gm every 4 hours until temperature has been normal for 48 hours then 0 5 Gm every 4 hours until convalescence is assured Crystalline sulfathiazole or sulfanilamide should also be used locally distributed evenly over the wound surface using 0 1 Gm per sq in, not to exceed 10 Gm in a single 24 hour period Polyvalent gas bacillus antitoxin may be used if necessary 20 000 40 000 units or more is given intravenously supplemented if necessary by intramuscular injections These doses may be repeated in 12 to 24 hours depending on symptoms and response to initial dosage

7 Staphylococcic infections Small furuncles should be treated by application of hot wet dressings until fluctuation develops Lesions which resist spontaneous evacuation after becoming fluctuant should be incised and drained and crystalline sulfathiazole applied locally to the incised area Large boils and carbuncles are treated similarly but in addition sulfathiazole or sulfadiazine is administered orally with 4 Gm as the initial dose followed by 1 Gm every four hours for seven days Dosage of locally applied crystalline sulfathiazole should not exceed 10 Gm in 24 hours

In treatment of diffuse cellulitis, lymphangitis and acute osteomyelitis the affected part should be immobilized and elevated continuously Sulfathiazole or sulfadiazine is given, with initial dose 4 Gm followed by 1 5 Gm every four hours as long as evidence of s ng

infection continues with improvement dosage is reduced to 1 Gm every four hours for at least seven days Surgery is performed when indicated followed by locally applied crystalline sulfathiazole

Staphylococcic bacteremia is treated with sulfathiazole or sulfadiazine Initial dose is 4 Gm orally followed by 1 5 Gm every 4 hours until temperature has been normal for 48 hours whereupon 1 Gm every 4 hours is given for 14 days All areas of focal infection should be located and drained if possible

In chronic staphylococcic suppuration as in chronic *osteomyelitis drainage should be maintained by vaseline* gauze packs until sequestration of necrotic tissue has occurred and the wound is covered with clean granulations Oral administration of sulfathiazole or sulfadiazine is of some value as is also local application of crystalline sulfathiazole

8 Peritonitis (secondary to appendicitis or bowel perforation) Sulfanilamide crystals 4 8 Gm should be applied to the peritoneum in the immediate area exposed at operation and to the layer of the abdominal wound during closure Parenterally 150 cc of 1 per cent sulfanilamide solution should be given every six hours by hypodermoclysis starting before or immediately after operation This dosage is continued for two days If progress is satisfactory at that time dosage may be reduced to 120 cc (1 2 Gm) every six hours As soon as oral feedings are allowed sulfanilamide may be given orally 1 Gm every four hours Treatment beyond the sixth postoperative day is usually unnecessary If no sulfanilamide is implanted locally the initial dose of the solution by hypodermoclysis should be 400 cc

9 Urinary tract infections in adults Any urinary tract obstruction greatly militates against successful use of sulfonamides and other compounds in treatment of urinary tract infections When such obstruction is present therefore every effort should be made to eradicate it Fluid intake should be so adjusted that urine output

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demonstrated that sulfadiazine is a powerful bactericidal agent against hemolytic streptococci whether the drug was added directly to whole defibrinated blood in vitro or whether it was given orally The bactericidal effect was present in dilutions as low as 2 5 mg per cent and was enhanced by presence of natural or acquired anti bodies When the relative merits of sulfanilamide and sulfadiazine were compared in vitro it was clear that sulfadiazine was always more effective in killing hemolytic streptococci

The evidence suggests that sulfadiazine will be supe rior to sulfanilamide in treatment of hemolytic streptococcic infections in man Since it is relatively nontoxic is readily absorbed from the gastro intestinal tract and diffuses into the serous sacs and meninges in high concen tration it would seem to be preferable to sulfanilamide in treatment of hemolytic streptococcic infections

Penicillin Chemotherapy of Mice Infected with Staphylococcus Aureus H M Powell and W A Jamieson[8] (Lilly Research Laboratories Indianapolis) infected mice intraperitoneally with staphylococcus cultures treated one group with penicillin a second with sulfathiazole and left a third group as controls A summary of all mice on all doses of the various cul tures used revealed that 69 per cent of the penicillin treated mice survived 45 per cent of the sulfathiazole treated mice survived and 23 per cent of the control mice survived. After discounting 85 survivors from each of the therapeutic groups it was found that ap proximately 60 per cent (163) of a possible 275 mice were saved by penicillin and 30 per cent (79) of a possible 275 mice were saved by sulfathiazole giving a 2 1 ratio in favor of penicillin

Further Observations on Penicillin are reported by E P Abraham E Chain C M Fletcher A D Gard ner N G Heatley M A Jennings and H W Florey[9] (Oxford Univ) The bacteriostatic power of penicillin

(8) J I dia M A 35 361 36 J ly 1942
(9) L n et 2 177 189 A g 16 1941

is about 1,000 cc per day If signs of renal impairment exist doses of the drug employed should be reduced and the blood level of the drug should be determined daily so that concentrations of more than 10 mg per cent can be avoided Urine cultures should be made by placing 5 cc urine on a blood agar slant containing 2 mg per cent of para aminobenzoic acid This should be incubated for five days before being discarded as sterile

Sulfadiazine is the drug of choice in infections due to Escherichia coli, Aerobacter aerogenes Shigella dispar and other gram negative organisms belonging to the so called coli typhoid paratyphoid group One Gm is given orally every four hours until definite clinical improvement occurs whereupon dosage is decreased to 1 Gm four times daily until the urine is clear and two negative cultures have been obtained The drug is then stopped and after one week the urine is recultured Sulfathiazole is the second drug of choice sulfanilamide the third dosage is the same for all

In infections due to Staphylococcus aureus sulfathiazole or sulfadiazine is the drug of choice The therapeutic regime is the same as that outlined for Escherichia coli infections Sulfathiazole is the drug of choice in infections due to Pseudomonas aeruginosa and Bacillus proteus dosage is the same as above

Infections due to enterococcic organisms (Streptococcus faecalis) do not respond to sulfonamide drugs Specific treatment is conducted with ammonium mandelate giving 3 Gm four times daily for five to seven days Sufficient ammonium mandelate should be administered to keep the urine pH at 5 or below The drug should be stopped if violent nausea or vomiting appears

If organisms other than those considered are the cause of urinary tract infection either sulfadiazine or sulfathiazole should be used in dosage as outlined above

Sulfadiazine Study of Its Effect on Hemolytic Streptococci Experiments conducted by Charles H Rammelkamp and Chester S Keefer[7], (Boston Univ)

(7) Ann Int M d 16 659 66 Ap ll 194

ylococci is not antagonized to any appreciable degree by hydrolytic protein breakdown products or products of tissue autolysis or pus substances which annul completely the bacteriostatic action in vitro of the sulfonamide drugs This is again of significance in the treatment of suppurating wounds and makes possible the successful treatment of infections in which abundant production of pus occurs

Substances which are not bactericidal but only bacteriostatic depend largely for their curative properties on the activity of leukocytes which deal with the organisms while the latter are prevented from multiplying Observations indicate that penicillin at 1 500 does not appear to embarrass leukocytic activity in vitro This is in contrast with its complete bacteriostatic effect on staphylococci and streptococci in vitro at dilutions of at least 1 1 000 000 It is clear that leukocytes will remain completely active in any concentration of penicillin likely to be reached after intravenous injection

During the course of some therapeutic trials in human infections it has proved possible to secure and maintain a bacteriostatic concentration of penicillin in the blood without causing any toxic symptoms After intravenous administration a large proportion of the active substance can be recovered from the urine and used again

Penicillin was given intravenously to five patients with staphylococcic and streptococcic infections and by mouth to one baby with a persistent staphylococcic urinary infection It was also applied locally to four patient with an eye infection In all these cases a favorable therapeutic response was obtained

Comparative Antibacterial Activity of Penicillin and Gramicidin Tissue Culture Studies reported by Dorothy H Heilman and W E Herrell[1] (Mayo Clinic) indicate that purified gramicidin and a highly concentrated preparation of penicillin exhibit the same order of activity against strains of gram positive cocci

(1) P St ff M t M y Cl 17 3 13 7 M y 27 194

against streptococci and staphylococci is as great as or greater than that of the most powerful antiseptics known Yet penicillin is not an antiseptic it exerts no direct immediate bacterial action This was borne out by two observations (1) The oxygen uptake of staphylococcic suspensions was not inhibited to any measurable degree by addition of penicillin to a final concentration of 1 1 000 over three hours (2) After incubation at 37 C for 24 hours a staphylococcic suspension in broth containing 1 1 000 penicillin grew large numbers of colonies on subculture The only trace of lethal effect observed was an acceleration of the death rate of small numbers of streptococci in Ringer s fluid containing 1 50 000 penicillin compared with the rate in pure Ringer s fluid

In mode of action penicillin resembles the bacteriostatic sulfonamide drugs but comparison reveals certain significant differences The bacteriostatic power of penicillin against streptococci and staphylococci is much greater than that of the sulfonamides even when these substances are tested under optimal conditions (small inoculum peptone free mediums, etc) Saturated watery solutions of sulfapyridine and sulfathiazole show no complete inhibition on an assay plate whereas penicillin at 1 500 000 gives an appreciable clear zone The action of penicillin on streptococci and staphylococci unlike that of the sulfonamides is influenced only to a minor extent by the number of bacteria to be inhibited Even when the culture mediums are inoculated with several millions of staphylococci or streptococci per cc of medium the multiplication of these organisms may be completely inhibited by penicillin in a concentration as low as 1 1,000 000 With smaller inoculums the inhibition will occur in even higher dilutions This property of penicillin is of great importance for the treatment of heavily infected wounds on which the sulfonamide drugs seem to have but little beneficial action The bacteriostatic power of penicillin against streptococci and staph

The effect of gramicidin is inhibited only to a small extent by serum tissue extracts or peptones of all substances tested the phospholipid phosphatidyl serine is the only one which has been found to be very inhibitory Many tissue constituents on the other hand inhibit the activity of tyrocidine and it is difficult to detect the effect of this substance on gram negative bacilli in peptone solutions

Tyrocidine immediately destroys the metabolic activity not only of bacterial but also of animal cells as recognized by loss of oxygen uptake of reducing ability and of acid production On the contrary these essential metabolic functions—even in the most susceptible cells—are unimpaired by gramicidin

It appears therefore that tyrocidine behaves like a general protoplasmic poison whereas the effect of gramicidin is of a much more subtle nature

The facts that gramicidin is effective in vivo when tested under appropriate conditions and that some attempts have been made to use it in therapy give special interest to a knowledge of its effect on animal cells Gramicidin does not seem to affect the growth and behavior of animal cells in tissue culture nor does it alter the oxygen uptake of polymorphonuclear leukocytes resuspended in buffer solutions Bull spermatozoa on the other hand are extremely susceptible to it as evidenced by loss of motility and modification of the metabolism Both gramicidin and tyrocidine are hemolytic the hemolysis by gramicidin however though caused by a much smaller amount is slow and entirely prevented in vitro by low concentrations of glucose and mannitol Both compounds are highly toxic to dogs and mice when injected into the blood stream It is possible that the hemolytic action of gramicidin may contribute to its toxicity in the blood stream On the other hand gramicidin either in the purified form or mixed with tyrocidine in tyrothricin appears to exhibit less toxicity when applied locally for instance on mucous membranes

There are however well marked differences in the selective bactericidal activity of these substances Both act on bacteria at a slow rate Although small amounts of gramicidin and penicillin may be only bacterio static, there is evidence that both substances may be bactericidal under certain conditions Neither sub stance enhances or inhibits the bactericidal activity of the other

Bacteriostatic and Bactericidal Agents Obtained from Saprophytic Micro Organisms are discussed by R J Dubos (New York City) with particular consid eration of gramicidin and tyrocidine Despite the com mon origin of these substances from *Bacillus brevis* and the fact that both substances are polypeptides and be have as surface active substances, gramicidin and tyro cidine differ in both chemical properties and biologic activity Tyrocidine when tested in buffer solutions in the absence of serum tissue extracts or peptones affects both gram positive and gram negative microbial species Gramicidin is completely inactive against gram negative bacilli moderately active against meningococci and gon ococci and highly inhibitory to practically all the gram positive species so far tested with the exception of acid fast bacilli Noteworthy is the isolation from susceptible bacterial species of variant forms which are more re sistant to gramicidin and which remain resistant even after repeated subcultures in mediums free from the substance these resistant forms are readily obtained from staphylococcus cultures and much less so from group A streptococci

Gramicidin never causes lysis even of the most sus ceptible organisms Tyrocidine lyses many bacterial species, evidence indicates, however that this lytic effect is not a direct one but only a secondary autolytic proc ess which follows the death of the cell and which occurs only in species endowed with active autolytic enzymes e g, pneumococcus and staphylococcus

(2) J Ped at 19 588 595 N embe 1941

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Tyrocidine immediately destroys the metabolic activity not only of bacterial but also of animal cells as recognized by loss of oxygen uptake of reducing ability and of acid production On the contrary these essential metabolic functions—even in the most susceptible cells—are unimpaired by gramicidin

It appears therefore that tyrocidine behaves like a general protoplasmic poison whereas the effect of gramicidin is of a much more subtle nature

The facts that gramicidin is effective in vivo when tested under appropriate conditions and that some attempts have been made to use it in therapy give special interest to a knowledge of its effect on animal cells Gramicidin does not seem to affect the growth and behavior of animal cells in tissue culture nor does it alter the oxygen uptake of polymorphonuclear leukocytes resuspended in buffer solutions Bull spermatozoa on the other hand are extremely susceptible to it as evidenced by loss of motility and modification of the metabolism Both gramicidin and tyrocidine are hemolytic the hemolysis by gramicidin however though caused by a much smaller amount is slow and entirely prevented in vitro by low concentrations of glucose and mannitol Both compounds are highly toxic to dogs and mice when injected into the blood stream It is possible that the hemolytic action of gramicidin may contribute to its toxicity in the blood stream On the other hand gramicidin either in the purified form or mixed with tyrocidine in tyrothricin appears to exhibit less toxicity when applied locally for instance on mucous membranes

or wounds or when injected by subcutaneous intramuscular or intrapleural routes

As yet *insufficient information exists to warrant an* opinion concerning the potential value of gramicidin or penicillin the soluble principle of Penicillum notatum as chemotherapeutic agents However both penicillin *and gramicidin have revealed new types of organic com* pounds endowed with remarkable bacteriostatic and bac tericidal activity An exact knowledge of the chemical structure of these new compounds and especially of the *molecular groups to which they owe their biologic activ* ity may present valuable clues for the synthesis of new substances which it is hoped will be of greater prac tical value than the naturally occurring substances

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MISCELLANEOUS CONDITIONS

Behavior of Some Common Fevers in Wartime An *editor[3] reports that no major influenza epidemic de* veloped in the winter of 1940 1941 and with the ex ception of cerebrospinal fever the course of infectious diseases since the outbreak of the war has been satis factory The table shows the number of notifications reported for five diseases in 1940 compared with the years preceding the war Scarlet fever was falling in the pre war period and this downward trend continued to a level substantially below recent previous experi ence Its course during 1940 was however rather un usual Rather than exhibiting the usual decline from early spring until autumn when the customary sea sonal rise occurs notifications in 1940 were extremely low in the earlier part of the year but began to rise at the beginning of April so that at the time of the nor mal minimum there was but little difference between the two curves School closure in the early days of the war and subsequent reopening may have caused this change At the beginning of 1941 notifications were

(3) Lancet 1 641 May 17 1941

falling rapidly and at the latest date were again well below the average of those for the years 1935 to 1939

Diphtheria presented a similar course notifications being low in the first half of 1940 and rising to the usual level in the latter half The enteric fevers typhoid and paratyphoid were in total somewhat above the 1935 1939 level but the position is reassuring in view of conditions extant Acute anterior poliomyelitis and polio encephalitis were in total rather above the normal level in 1940 though less than in the epidemic year

NUMBER OF NOTIFICATIONS IN ENGLAND AND WALES

	1935	1936	1937	1938	1939	1940
Scarlet fever	120 532	101 896	95 832	9[illegible] 413	78 [illegible]01	65 547
Diphtheria	65 494	58 205	61 435	65 7[illegible]0	47 710	46 680
Enteric fever	1 781	2 566	[illegible] 145	1 358	1 5[illegible]4	2 835
Poliomyelitis and polio-encephalitis	700	586	861	1 58[illegible]	836	1 106
Cerebrospinal fever	875	1 011	1 157	1 293	1 508	12 793

F m th R gist G l w kly po t

1938 Cerebrospinal fever is the only condition the incidence of which has been far in excess of previous experience The year s total for 1940 was nearly 13 000 cases or more than tenfold the normal experience Initial reports for 1941 indicate that the epidemic will be on a smaller scale than that of 1940 though still relatively *large and widespread*

Problem of Certain Tropical Diseases in the War is discussed by Henry E Meleney[4] (New York Univ) Most important among these is malaria which clinically comprises three separate diseases the benign tertian and quartan types which cause great disability but few deaths and the malignant tropical estivo autumnal type which may simulate many other diseases is often fatal and is frequently associated with severe complications such as blackwater fever and profound anemia

(4) New E gl d J Med 2 7 159 162 J ly 30 194

Diagnosis is sometimes difficult because of bizarre manifestations and because the parasitized erythrocytes adhere to the capillary walls during the second 24 hours of the asexual life cycle and may not be found in the circulating blood Therefore, in every case of illness in the Tropics malaria must be constantly borne in mind, and daily blood films must be made until malaria is diagnosed or excluded

Treatment of malaria is not simple Even after a supposedly complete course of treatment with quinine or atabrine relapses occur in about 50 per cent of cases of tertian and quartan malaria and in about 20 per cent of estivo autumnal cases In the latter, the early relapse may be fully as severe as the first attack The recent tendency is to use short vigorous treatment courses for the acute attack and to treat relapses as they occur, but many still believe that treatment should be continued for 8 to 10 weeks a procedure difficult to conduct among troops on active service

A higher incidence of typhoid fever must be anticipated unless emergency sanitation is more efficient than in World War I and unless the troops are educated to protect themselves from polluted water and food Likewise dependent on rigid sanitation and troop education is prevention of bacillary and amebic dysentery and the milder epidemic diarrheas such as the salmonella staphylococcus toxin and water pollution diarrheas all of which may disable essential units during crucial periods Cholera must not be overlooked

Gonococcus Bacteremia with Joint and Skin Manifestations is reported by Ruth C Foster[5] (Madison Wis)

Girl, 20 pre ented multiple joint pains stiffness, generalized myalgia and fever At four to six day intervals there occurred elevation of temperature as high as 104 2 F, accentuation of joint pains and a maculopapular eruption on the chest, back arms and legs The eruption consisted of discrete, reddish purple maculopapular lesions about 0 3 mm in diameter, which later developed vesicles. Associated with

( ) Ann I t Med. 16 1018 10 May 194

these epi odes was leukocytosis as high as 43 450 principally neutrophilic The che t and abdomen were normal The gonococcus was isolated from blood cultures taken during febrile reactions She was given 3 Gm promin intravenously and within three hours was afebrile and asymptomatic This was followed by oral sulfanilamide therapy for 11 days Smears and cultures remained negative during 18 months of observation There has been no evidence of endocarditis at any time.

New Localities for Trypanosoma Cruzi Chagas in Southwestern United States are reported by Sherwin F Wood[6] Man commonly comes in contact with tria toma the vector of Trypanosoma cruzi in many parts of the Southwest for at least two months of the year (May and June) This contact is not of recent origin for communications from three mining engineers in Arizona indicate that they have come in contact with these bugs all their lives Contact with the bugs has been so constant that many persons think nothing of their presence This indicates that it is only a matter of time before Chagas disease in man will be detected in the United States

It has been recently shown that an edematous condi tion of the face affecting particularly the eyelids is a valuable diagnostic symptom of this disease in Argen tina Mazza reports that unilateral palpebral edema was present in 68 per cent of 487 human cases in Argentina Information from a mine near Congress Yavapai Co Ariz indicating the occurrence of this condition one to two weeks after being bitten by the insect suggest that man may have contracted trypanosomiasis there Fur ther evidence of possible human infection in Arizona is supported by the following facts (1) recovery of in fected Triatoma longipes from human habitations (2) long association of man with several species of triatoma capable of transmitting the disease (3) great abun dance of the bugs during warmer periods of the year causing them to be known as a common insect (4)

(6) Am J Hyg Sect C 34 1 13 July 1941

apparent tendency for adult triatoma to seek man for food (5) tolerance by man of these pests while living in loosely constructed houses or sleeping unprotected outdoors and (6) inability of man to control sources of these insects especially wood rat nests

Rat Bite and Haverhill Fevers The significant clinical features of rat bite and Haverhill fevers are described by Tom Kirkwood (Lawrenceville) and C G Stoll[7] (Sumner) Recognition of these obscure febrile conditions is important in order that neoarsphenamine therapy may be instituted early This drug is virtually specific in Spirillum minus infections and gives promise of being useful in Haverhill fever

In rat bite fever caused by Spirillum minus the wound usually heals by first intention After a 5 25 day incubation period (average 14 days) the initial wound becomes red and painful blisters may appear and ulceration eventually occurs The ulcer has a clean surface and a serous discharge thereby resembling an extragenital chancre and heals slowly Pus in the discharge often indicates that some other organism is causing the disease or is acting as a secondary invader These local changes are accompanied by lymphangitis with regional adenopathy similar to that in tularemia A hard chill usually occurs about the time the local changes are noted This is accompanied by generalized muscular aching and pain Temperature rises rapidly to 104 or 105 F lasts two or three days and then quickly drops to normal or below and is followed by a drenching sweat The chills recur at three to seven day intervals and may go on for months if the disease is not recognized and properly treated Soon after onset of the disease the typical eruption appears It consists of large reddish purple maculopapular spots which appear on the skin at various places including the face after each chill These areas vary in size from a dime to 2 or 3 in in diameter As the fever subsides

(7 Illinois M J 80 141 14 August, 1941

after each chill the eruption gradually fades only to recur after the next chill Between chills the patient may feel very well but as the disease continues weakness and emaciation become more marked until in unfavorable cases exhaustion supervenes Mortality is 2 10 per cent

In sporadic Haverhill fever the etiologic agent of which is Haverhillia multiformis the rat bite usually heals promptly and rarely shows any marked subsequent reaction After a three to five day incubation period the invasion begins Onset is sudden and generally severe Nausea and vomiting appear early Also prominent are chills backache general myalgia and headache Initially the temperature may reach 105 106 F and frequently causes delirium In two to five days an abrupt fall in temperature occurs with marked general symptomatic improvement A rash occurs in practically all cases appearing on the second to the fourth day of the disease This rash is rubellaform to morbilliform in appearance and occurs chiefly on the extensor surfaces of the extremities and about the joints In severe cases distribution is more general The rash lasts for one to eight days and desquamation may follow A secondary temperature rise occurs one to three days after the initial decrease and is quickly followed by polyarthritis The arthritis commonly occurs on the fourth or fifth day of illness but it has been noted as early as the second and as late as the thirteenth day It may persist for weeks or months the fever curve simulating that of typhoid fever but with greater diurnal variations During this period the disease is easily confused with acute rheumatic fever Sore throat occurs in half of the cases usually appearing about the eighth day Bronchitis may be present Mortality is low

New Organic Antimonial for Treatment of Kala Azar by Intramuscular Injection—Neostebene Upendra Nath Brahmachari[8] (Carmichael Med College

(8) J T p M d & Hyg 44 158 160 De 1 1941

Calcutta) records attempts at further advances in the treatment of kala azar by the intramuscular injection of a new organic antimonial neostebene It is a derivative of P amino phenyl stibinic in organic combination and is an amorphous powder grayish white and fairly soluble in water Its antimony content is nearly 41 per cent A series of 10 cases is reported of which the following is illustrative

Man 35 was hospitalized March 25 He had had irregular intermittent fever for 1½ years and diarrhea for 6 months The spleen and liver were palpable 5 in and 1½ in below the costal margins respectively On admission blood examination showed hemoglobin content 45 per cent, erythrocytes 2 200 000 leukocytes 3,437, polymorphonuclear leukocytes 66 per cent lymphocytes 32 per cent eosinophils 2 per cent The aldehyde test was strongly positive Splenic puncture revealed Leishman Donovan bodies

Neostebene, 0 1 Gm was given twice weekly, total dosage was 3 5 Gm The temperature became normal after eight injections On May 31 the spleen extended 1½ in below the costal margin the liver was not palpable Blood examination showed hemoglobin content 65 per cent erythrocytes 3 800 000 leukocytes 5 000 polymorphonuclear leukocytes 70 per cent lymphocytes 28 per cent eosinophils 2 per cent No Leishman Donovan bodies were found on splenic puncture

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GENERAL CONSIDERATIONS

Possible Dangers of Transmission of Disease by Airplane are discussed by Waddie P Jackson[9] (M C, U S N R) The diseases chiefly concerned are cholera, plague smallpox typhus fever yellow fever, malaria and dengue Incubation periods of these diseases are 2 14 days For cholera, it is 2 5 days for plague 2 6 days for yellow fever 3 6 days for typhus fever 5 12 days and for smallpox 10 14 days The usual flight traveling time is less than a week so that a traveler can easily become infected just before departure and break out with the disease a day or so after reaching his destination Thus the human being may be

(9) U S Nav M B ll 40 115 123 January 1942

an important carrier of infection during the incubation period of numerous serious epidemic diseases

It has been proved that airplanes transport mosquitoes and other insect vectors of dangerous diseases The prevalence of insects in the cabins of aircraft varies with the site of the airdrome i e whether it is on land or water and the distance it is from the shore There are many places in the planes where mosquitoes may not be disturbed by air drafts such as under seats baggage compartments etc Recent investigations indicate that interior disinfection of aircraft is insufficient because the mosquitoes and other insects may find safe harborage in the space between the outer and the inner lining of the aircraft or in the hollow wings The exterior of aircraft offers many hiding places such as the space for retracted undercarriage and various grooves and rivet holes

It has been reported that after inspection of all incoming aircraft at Miami from Central America South America and Mexico in 1938 of the 398 aircraft examined 187 contained dead and live insects of various species Of the 651 insects recovered 166 were alive despite the fact that the planes were sprayed carefully with insecticide one half hour before landing as required by regulations Of the 651 insects found 45 were mosquitoes 40 dead and 5 alive No Aedes aegypti were found However Aedes aegypti were captured and identified from planes coming from Cuba and other Southern ports

Of the diseases enumerated yellow fever and malaria assume greatest significance There is little assurance that tropical or subtropical communities are under sufficient control to prevent widespread transmission of a disease like yellow fever once it enters that community This danger is even more apparent today since there are now known to be vectors of yellow and malaria fever other than the Aedes aegypti and Anopheles quadrimaculatus

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Man 55 was hospitalized March 25 He had had irregular intermittent fever for 1½ years and diarrhea for 6 months The spleen and liver were palpable 5 in and 1½ in below the costal margins, respectively On admission blood examination showed hemoglobin content 45 per cent erythrocytes 2 200 000 leukocytes 3,437, polymorphonuclear leukocytes 66 per cent lymphocytes 32 per cent eosinophils 2 per cent The aldehyde test was strongly positive Splenic puncture revealed Leishman Donovan bodies

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(9) U S Naval M Bull 40 115 1 3 January 1942

For seasonal adynamia with excessive fatigability the author gave 10 capsules a day (5 in the morning and 5 in the afternoon) for 5 to 20 days and at times a daily intramuscular injection of 1 ampule for 20 days. Results were excellent in 18 of 20 patients treated; the other 2 were objectively improved but not subjectively. Fifteen asked for more C phos because it made them feel so much stronger.

C phos must be given early, immediately after temperature is normal in grip and at the first signs of deficiency of neuromuscular tonus in seasonal adynamia. Dosage must be high from the beginning to obtain rapid and durable results.

The author gave C phos to soldiers for 15 days before a test march in hilly country: 10 capsules daily for 10 days and 15 capsules daily for 5 days. Intensive training was well supported, fatigability was decreased, there were no collapse or muscular cramps, no cerebral or cardiac hyperexcitement and especially no subsequent depression of the *neurovegetative system* often seen after intense and prolonged efforts.

Disease Outbreaks from Water, Milk and Other Foods in 1939 are reported by A. W. Fuchs (U. S. Pub. Health Service) and are compared with those for 1938.

The most striking fact is that other foods were a far more prolific source of outbreaks than were milk or water, particularly in 1939, when other foods were responsible for nearly 60 per cent of all outbreaks reported, as compared with approximately 40 per cent in 1938. The increase for 1939 may represent better reporting rather than an actual rise. In 1939, outbreaks from other foods likewise involved more cases and more deaths than did those due to water or milk. The excess of total cases in 1938 over 1939 was the result of a single water borne outbreak of gastro-enteritis involving 23,250 cases, which occurred in one large city.

The largest outbreak reported for 1939 was one of

The proper authorities should see that all possible means known to prevent the introduction of those diseases should be used especially (1) more widespread vaccination against yellow fever among those who travel in yellow fever regions when the products become available for common use (2) more liberal vaccination against cholera in cholera infested areas (3) more perfection in disinfecting airplanes and (4) more careful and thorough inspection of passengers and cargoes from planes coming from any of the infected areas This last point is especially to be emphasized because as air travel becomes more and more popular and more within economic reach of the lower social strata where these diseases are more prevalent the dangers will become still greater

Use of C Phos for Troops P Sauser Hall[1] (Geneva) stresses the importance in modern armies of shortening convalescence of soldiers who have had a relatively benign infectious disease such as grip It is also important to have a stimulant which will help the soldier to make a strenuous effort at any time and under any circumstances without exposing him to objectionable secondary effects Theoretical considerations of the role of phosphorus in the body and animal experiments led to creation of C phos which is composed of sodium a oxybenzylphosphinite and ascorbic acid The author has studied the influence of this substance on postgrippal asthenia seasonal adynamia and forced military marching

For postgrippal asthenia the author gave a daily intramuscular injection of 2 ampules of C phos for five or six days with good results Convalescence was shortened general condition improved rapidly and functional capacity was increased Half of 41 patients were so much better after the third or fourth injection that they could be returned to their unit under ambulatory treatment In a few treatment was continued with 40 to 60 capsules at the rate of 10 a day

(1) Schweiz med Wchnschr 19 199 Feb 14 194[illegible]

year study in the Germantown Friends School and a one year study in the Swarthmore public schools there has been no epidemic spread of contagion among the highly susceptible groups of children of the primary schools in irradiated atmospheres although epidemic spread has occurred among less susceptible groups of older children in nonirradiated atmospheres

During the first experimental year seven introductions of mumps into the irradiated and seven into the unirradiated classrooms of the primary department at Germantown were followed by 2 and 12 cases respectively During the second year 32 cases of mumps occurred in the unirradiated upper classrooms with only 1 case appearing in the irradiated primary classes While mumps is a disease of lower incidence than measles or chicken pox and susceptibility therefore extends into the older age groups there is no selective action for the older ages the peak incidence being among the 7 8 year groups In the five years at Germantown and the nine years at Swarthmore prior to irradiation the primary classes enjoyed no such exemption

During the third experimental year 21 exposures to chicken pox of classes in the irradiated atmospheres resulted in only 7 secondary cases but exposure of one class for a relatively short time on each of four successive days in an unirradiated atmosphere with a missed case resulted in a static type epidemic involving 15 of the 16 susceptibles in the class The susceptibility to chicken pox in the upper grades was so low that spread could not have been expected

The most convincing confirmation of the hypothesis that epidemic contagion is spread through the medium of confined atmospheres and can be prevented by radiant disinfection of air comes from the results of the 1941 measles epidemic at Germantown and Swarthmore Data show that the attack rates among susceptibles were among the primary irradiated classes 14 5 per cent at Germantown and 15 7 and 9 per cent at Swarthmore

bacillary dysentery occurring in a state institution at Marcy, N Y, in which 609 of the 2 321 patients exposed were affected through either milk or food prepared by three carriers This outbreak is listed under unidentified vehicles The largest outbreak from milk and milk products was one of septic sore throat at Catskill and Saugerties, N Y involving *546 customers of a* raw milk dealer handling 10 per cent of the total supply The infection was traced to a cow with acute mastitis from which hemolytic streptococci of the human type were isolated The largest outbreak from water

TOTAL OUTBREAKS CASES AND DEATHS BY VEHICLES 1939 AND 1938

VEHICLE	1939			1938		
	Outbreaks	Cases	Deaths	Outbreaks	Cases	Deaths
Water supplies	43	2 254	3	48	31 693	17
Milk and milk products	41	2 [illegible]09	7	42	1 685	27
Other foods	148	3 782	12	70	2 247	25
Unidentified vehicles	17	1 703	6	8	882	3
Total	249	9 748	28	168	36 507	72

supplies occurred at Minneapolis Approximately 400 cases of gastro enteritis and 2 cases of typhoid fever were reported among employes of office buildings using water from drilled basement wells which were found to be contaminated by sewage The largest outbreak from other foods was one of gastro enteritis in Monroe County, N Y in which 320 of 400 guests at a banquet were affected Neither the identity of the food nor the manner of contamination could be ascertained

Environmental Control of Epidemic Contagion. W F Wells, M W Wells and T S Wilder[3] (Univ of Pennsylvania) describe an epidemiologic study of radiant disinfection of air in day schools During a four

(3) Am. J Hyg 3 97 1 0 Jan ry 194

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school branches among the upper unirradiated classes 55 3 per cent at Germantown and 51 8 per cent at Swarthmore *Time relationships of the epidemic* suggested infiltration from the upper schools into the primary classes rather than epidemic spread within the latter It was also shown that in each of the three primary schools the susceptibility was considerably higher at the end of the epidemic than it was in the upper classes at the beginning Certainly the epidemic patterns in the two schools were strikingly different from any previous experience

With these results one might almost suspect a virus strain with an affinity for older ages The 6 year group in Philadelphia, however showed as usual the highest incidence Likewise at a private day school for boys a short distance from the Germantown school having pupils of essentially the same social class the primary classes suffered most heavily Among 95 boys in the first four grades (susceptibility unknown) there were 47 cases (49 5 per cent) among 391 boys in the eight upper classes there were 38 cases (9 7 per cent) At the Germantown Friends School, 12 6 per cent of the pupils in the primary department were attacked and 23 2 per cent of the pupils in the upper classes

Equally favorable results would not necessarily follow radiant disinfection of schools chosen at random The prevention of air borne infection among *intermittent aggregations* necessitates both an effective means of control and the employment of that means within the particular atmosphere in which the infections actually were transferred

[It is difficult to escape the conclusion from this excellent study that ultraviolet radiation is of definite value in the sterilization of air and thus in the prevention of contagious di ea e —Ed]

Allergy and Resistance to Infection with considera tion of the underlying mechanisms, are discussed by Frederick Smith[4] (McGill Univ) The immunity in

(4) Am J M Sc 0 447 456 Septembe 1941

tuberculosis and infection in general subsequent to primary infection has been more or less completely related to the allergic state but recently increasing doubts have been cast on the allergic reaction as a mechanism whereby invading bacteria are localized or destroyed Opie states that in the process of local fixation it is not possible to estimate the relative importance of antibodies of phagocytes and of the inflammatory reaction itself Rich feels that the factors which govern resistance to infection are distinct from those concerned in allergic inflammation even though both attributes result from the same exposure This does not imply that hypersensitivity does not modify the operation of immunity for it has been pointed out that increased transudation from the blood vessels must by dilution help to neutralize the injurious effects of the products of bacterial disintegration in the hypersensitive body The same process clearly makes available to the tissues whatever factors of protection circulate in the blood Conversely those very products of bacterial disintegration in comparable concentration would not cause necrosis of normal nonsensitized tissue

Many earlier writings concerning the relation between allergy and immunity dealt with the events which follow parenteral introduction into an animal of heterologous protein The identity of the immune body responsible for anaphylactic sensitization and for the various in vitro immunity tests was established and it became commonplace not only to state that hypersensitivity is a stage in the development of immunity but to transfer the reasoning from inert molecular protein to bacterial allergy and resistance to living self propagating infective agents The correlation may extend to these bacterial components which behave after the fashion of heterologous proteins i e yield humoral antibodies passively sensitize the guinea pig uterus and exhibit an immediate hypersensitive response

Micro-organisms are complex chemical entities Dur

ing infection the tissues may become sensitized to both polysaccharide and protein Evidence indicates that the delayed tuberculin type of hypersensitivity due to the protein of micro organisms is unaccompanied by humoral antibody and cannot be passively transferred to normal animals It is achieved only by the introduction of intact bacteria dead or alive Hypersensitivity produced by the injection of bacterial proteins conforms to the anaphylactic type and while the tissues react violently and immediately to that protein they will not react hypersensitively to the injection of intact bacteria This type of experiment has no relation to bacterial allergy *in which condition an antibody mechanism is predicated* only on the specificity of the reaction and the fact of desensitization

Hypersensitivity is a property of the individual cell Cells from the blood and fixed tissues of tuberculous animals are distinctly more susceptible to the toxic action of tuberculin than are normal cells This raises the question of the value of the increased phagocytic capacity of mononuclears derived from actively tuberculous or vaccinated guinea pigs for tubercle bacilli This cellular hypersensitivity must militate against survival of the phagocytic cells

By contrast the allergy which develops to bacterial polysaccharide is of the immediate anaphylactic type and usually is accompanied by circulating antibody In *this type of sensitivity the individual cells in tissue culture* are not affected by the addition of specific antigen This is congruent with the view that local anaphylaxis depends on a precipitin reaction and serves to fix the antigen *within the tissue spaces Type specific antibody* without the intervention of inflammation likewise fixes the pneumococcus Nevertheless the rapid inflammatory response may support the mechanism of resistance even though not the prime factor, by facilitating access to the tissue spaces of antibody and phagocyte

The tissue response in allergic inflammation (not

differ qualitatively from that due to acute inflammation produced by any irritant in the normal body The vascular and cellular changes are identical The consensus is that the normal sequence of polynuclear mononuclear cells is followed The actual physiologic stimulus which determines these changes is the liberation of histamine and leukotaxine

Thus the immune animal potentially possesses phagocytic and antibody mechanisms of resistance and two conditions of hypersensitivity by which specific inflammation can be provoked The question is whether these latter are essential or beneficial to the animal in its efforts to combat infections

The path of absorption of chemical substances from the tissues depends on the size of their molecules the smaller molecules are absorbed by the blood the larger by the lymphatics Bacteria travel from the tissues by the lymphatics rather than the blood This agrees with the observation that in freshly made wounds the blood vessels shut down and thrombose within a few minutes of the injury while the lymphatics remain patent for over 48 hours

Well established inflammation forms a mechanical barrier which limits the dissemination of bacteria and other particulate matter with a few exceptions depending on the variety and virulence of the organism Opie showed that in local anaphylactic inflammation the small blood vessels and lymphatics are injured and often undergo thrombosis Menkin has emphasized the importance of this lymphatic blockage in localizing infection

However when bacteria are introduced into the normal tissues of an animal dissemination may take place before sealing of the lymphatics or mobilization of leukocytes can occur The immediate fate of micro organisms which gain access to the tissues is determined by the dynamics of capillary and lymphatic function in the early stages of inflammation In the vascular bed the main changes are vasodilatation with an increase in

capillary pressure and permeability These are responsible for the increased capillary filtration and for the parallel increase in lymph flow and pressure Edema and increased lymph flow per se facilitate dissemination After a time the lymphatics become occluded by fibrin thrombi Menkin considers that retention of materials in an acutely inflamed area depends on the fibrin network formed in the edematous tissue spaces or in lymphatic vessels He showed, moreover, that the rapidity with which bacteria are walled off by this process is a function of the intensity of the injury they cause, and this in turn varies with the nature of the micro organism Menkin and Lurie hypothecate an intense degree of inflammation for localization and admit that minor degrees may aid dissemination This contrasts with the views of other protagonists of the allergic theory Wilson *et al* for example find that a mild degree of inflammation assisted guinea pigs to resist tuberculous reinfection a high degree was worse than no allergy at all'

Regarding the bearing this has on the inflammation of allergy Rich pointed out that the deposition of bacteria in an area that is already inflamed when the bacteria are introduced is not comparable to what occurs in a hypersensitive reaction when the inflammatory reaction must develop after they reach the tissues Bacteria spread rapidly from the portal of entry in the normal animal and the time required for an effective amount of inflammation to appear around invasive bacteria even in the allergic body in which the process is accelerated is distinctly longer than the time required for bacteria to spread from the site at which they lodge Rich showed that on injection of a mixture of two bacteria into an animal hypersensitive to one of them, even though it reproduced the time conditions of an accelerated hypersensitive inflammation in the previously normal tissues the spread of the bacteria to which the animal was not immune was *accelerated* rather than retarded It is

concluded that the primary localization is accomplished by the immune antibody which acts to hold the bacteria at the site until the leukocytes can emigrate to attack and destroy them Also allergic inflammation may be associated with a faster or slower rate of spread of tubercle bacilli than in normal controls

Many observations either indicate that inflammation is not required or fail to distinguish events occurring in an allergic animal from events due to the allergic states Rich and his co workers state that in pneumococcus immunity localization and destruction of the bacteria are carried out by antibodies and phagocytes and that hypersensitivity adds nothing to this effective immunity Lurie made quantitative determinations of surviving and metastasizing tubercle bacilli introduced into normal and sensitized (B C G) guinea pigs and rabbits He found marked inhibition in multiplication of the organisms in the cell free body fluids and noted the numerous unsuccessful attempts to demonstrate in vitro bactericidal properties of serum derived from animals immunized against tuberculosis Freund and Angevine observed rabbits pretreated with heat killed tubercle bacilli intracutaneously and concluded that virulent tubercle bacilli introduced by the same route multiply actively at the injection site during the period of retarded lymphatic dissemination and that the retardation is caused by local fixation and not by destruction of the organisms The conclusion was correct in the sense that ample numbers of the bacteria were present locally for spread to occur if the channels were open but their figures show as much interference with local multiplication as with dissemination in the immunized animals Lurie found sensitization of the rabbit to promote lymphatic spread

The spontaneous waning of tuberculin sensitivity with persistence of acquired immunity suggests their independence A varying ratio of the two components hypersensitivity and resistance to infection has been

shown to depend on the route of immunization Intravenous immunization with killed tubercle bacilli rarely induces tuberculin sensitiveness whereas subcutaneous inoculation establishes the same degree of immunity as well as hypersensitivity Using streptococci, allergy and resistance have been similarly dissociated Many have stressed the efficacy of intracutaneous inoculation in inducing hypersensitiveness Some, however, believe that allergy so induced is in part responsible for the early stages of the immune state and that the early phase represents a tissue immunity in which fully developed resistance is associated with humoral antibody It is difficult to reconcile this concept with the experimental characteristics of the tuberculin type of sensitivity

It has been shown that desensitization experimentally and perhaps clinically can abolish hypersensitivity and leave resistance intact Those who feel that allergy is unrelated to immunity accept these experiments at face value their critics find much with which to disagree Freund and Angevine would not accept tuberculin desensitization as proof of desensitization to intact bacteria believing that the many deaths in prolonged desensitization of vaccinated animals invalidated the experiments of Rothschild *et al* It seems natural that continued administration of large amounts of tuberculin should impair the health of well or sick animals In this respect Willis and Woodruff suggested that the ma[illegible] tion emaciation and ulcers of the skin which follo[illegible] daily injections of large doses of tuberculin may factors in bringing about the difference in tuberculosis in the desensitized and untreated

gested that (1) a slight to moderate degree of allergy at the time of infection is favorable to survival (2) a high degree of allergy is definitely unfavorable and (3) a very high degree of allergy is worse than no allergy at all Somewhat paradoxically they concluded that the higher the degree of sensitivity to tuberculin reached after injection the longer the survival time How this affects the fate of surviving bacteria is not clarified Regarding the question of desensitizing doses of tuberculin they raise again the question of their immunizing value despite numerous studies to the contrary and despite the fact that it is the question of the hypersensitive state which is at stake Tangentially they then question whether desensitization is complete anyway and suggest that repeated injection may maintain minor inflammatory reactions around each tuberculous focus with the result that dissemination of the bacilli is retarded and the rapid caseation which seems more liable to occur in the highly allergic animal is prevented

In tuberculosis tubercle formation is incited by the lipoid fraction of the bacillus Tissue culture studies show that necrosis in these tubercles is the result of contact of hypersensitive cells with tuberculoprotein The vascular changes accompanying inflammation are not essential to the process of caseation Quantitatively it is likely that the amount of tuberculoprotein necessary will vary with the degree of hypersensitivity of the individual cells and in general will require some multiplication of the bacteria if the number which gains access to a given site is small A given number of bacteria will do less damage in a normal than in a hypersensitive body and the effect can be minimized by desensitization Wilson and his co-workers believe desensitized animals live longer than controls and show less severe lesions because in the controls allergy has been allowed to develop to a point at which the very intensity of the reaction in the internal organs—particularly the lungs—proves prejudicial to life Henrici correctly emphasized the impor

tance of considering the site of the allergic reaction In the Koch phenomenon the organisms and the products of the reaction are cast off to the exterior when the same reaction occurs in the lung or kidney it may result in extension of the disease

Opportunity for exposure and sensitization increases with age and reasonably contributes to the age differences in both the acute and chronic disease, particularly if the portal of entry is the respiratory tract Lauche points out that lobar pneumonia which is rare in young infants may occur in the first few days of life and is increasingly frequent as infancy is passed He regards lobar pneumonia as the response of an allergic body having a partial immunity to the infecting type of organism sensitization of the infants being passively transferred in utero the adult being sensitized as a result of minor upper respiratory infections According to this view allergy to the pneumococcus plays a part in the development of pneumonia Reimann suggests that the tendency to recurrence of lobar pneumonia is due to persistence of this allergic state Recurrences have the same type distribution as first infections but the incidence of bacteremia and case fatality rate seems generally lower One explanation of this paradox of increased susceptibility and greater resistance is that the one depends on nucleoprotein sensitization and the other on antipolysaccharide antibody Opie believed that while allergy is not essential in the production of diseases like lobar pneumonia rheumatic fever and glomerulonephritis it may modify their course

Thus the consensus seems to be that hypersensitive inflammation is an important mechanism in resistance to infection Moreover in chronic diseases like tuberculosis, the tissue destruction is a manifestation of allergy This is not to deny the value of vaccines or first infection as an immunizing experience, nor is it necessary to debate the merits of these procedures The mechanisms of resistance differ widely for different infective agents

and in some diseases like tuberculosis there is no clear basis for the state of resistance Therefore it seems logical to conclude that allergic phenomena would differ vastly in importance in diseases like diphtheria pneumococcic infection and tuberculosis

Skin Eruptions Following Vaccination H D Chalke reports a case

A healthy soldier noted a small pimple on the wrist 11 days after primary smallpox vaccination on the opposite arm There was no history of previous skin disease There had been a moderate local reaction with a considerable erythematous zone and some edema of the arm Further papules appeared during the next seven days Three weeks after vaccination there was a fairly profuse eruption of superficial irregular vesicles ¼ 1 in in diameter many with central crusts There was little or no surrounding erythema Pruritus was not present Major distribution was on the forearms thighs and scrotal region During the ensuing week the vesicle dried completely and there was generalized crusting Twenty days after inception of the rash nothing remained but large irregular pigmented areas

Skin eruptions are an uncommon sequel of vaccination They tend to occur more often after primary vaccination than after revaccination Different types of postvaccination rashes have been reported These vary from the local erythema which is a constant accompaniment of successful vaccination to lesions which embrace either the affected arm or other parts Papulovesicular erythematous and serum type rashes have been described Difficulties in diagnosis may arise during a smallpox epidemic when vaccination performed late in the incubation period may modify but not prevent an attack of smallpox A certain similarity in distribution between variolous and nonvariolous lesions such as vaccinal lichen may increase these difficulties In Chalke's case and in others reported it is concluded that the rash was a toxemic manifestation occurring during the height of the vaccinal reaction i e between the ninth and fourteenth day

( ) J R y Army M C rp 7 54 8 N mbe 1941

Manufacture of Antibodies in Vitro Linus Pauling and Dan H Campbell[6] (California Inst of Technology) report that a protein solution with the properties of a specific antiserum to the triphenylmethane dye methyl blue has been made by treating a solution of bovine gamma globulin and the dye with alkali and then slowly neutralizing the alkali Some success has been obtained also in the formation of antibodies from other serum proteins and by other denaturation renaturation procedures By heating solutions of gamma globulin and antigen to 57 C for several days antiserums homologous to the antigens have been prepared This method has been used successfully with the azodye 1,3 dihydroxy 2 4 6 tri(para azophenylarsonic acid)benzene and with pneumococcus polysaccharide type III The antipneumococcus serums were found to precipitate the polysaccharide of type III but not those of types I and VIII and to agglutinate pneumococci of type III but not those of types I and II

Heterophile Antibody Reaction Caused by Bacterial Infection S Bornstein[7] (Beth Israel Hosp New York City) reports that a strain of Escherichia coli cultured from the blood of a patient with severe cystitis contained heterophile antigen Following bacteremia the serum gave a positive heterophile antibody reaction (1 1 600) The antibodies could be differentiated from those observed in serum sickness and in infectious mononucleosis and were of Forssman s type They disappeared rather quickly from the patient s blood and vanished partly from refrigerated serum specimens unlike the antibodies of infectious mononucleosis The Wassermann reaction was positive for some time and there was a temporary increase of iso-agglutinins

Animal experiments show that infection with bacteria containing heterophile antigen can increase the titer of heterophile antibodies in the serum The same can hap

(6) J Expe Med 76 211 220 Augu t, 194
(7) A n I t Med 16 47 -4 9 M ch, 194

pen in man The increase in antibody titer is ordinarily slight but can become marked The quick disappearance of antibodies from the blood and their lability in the specimen may account partially for the rarity with which heterophile antibody reactions of this kind are observed The antibodies here are of the same type as those in normal serums which suggests a relation between the fluctuating titers of these antibodies and infections

Studies on the Effect of Carcinogenic Hydrocarbons on Immunity Reactions in rabbits are described by C Hoch Ligeti[8] (Royal Cancer Hosp [Free] London) A difference was found between the effect of carcino genic hydrocarbons applied through a long period prior to immunization and of treatment with these hydrocar bons at the peak of immunity While the prolonged treatment previous to immunization did not seem to influence the ability to produce antibodies an injection at the peak of the immunity decreased markedly the amount of antibodies In all the immune serums the amount of antibodies gradually decreased about 10 days after the last injection of the antigen horse serum The progressive decline observed after injection of anthra cene given on the eighth day after the last injection of horse serum may be considered due to this but the sud den drop observed within 48 hours after injection of methylcholanthrene must be attributed to a special effect of this hydrocarbon

Improved Nonvirulent Rabies Vaccine is described by L T Webster and J Casals[9] (Rockefeller Inst) The vaccine is prepared from the brains of beagle dogs given intracerebral injections of mouse brain rabies virus Pasteur strain It is rendered nonvirulent by ex posure to ultraviolet light Four tests were made

1 The authors intracerebral mouse test was used Three 0 03 cc intraperitoneal doses of vaccine immun ized mice effectively To permit comparison of irradi

(8) B t J E pe P th 2 233 240 A gust, 1941
(9) Am J P b H lth 3 268 270 M h 194

ated vaccine with others designed for human treatment commercial phenolized and chloroformized vaccines and the irradiated vaccine were diluted to eliminate the effect of phenol and chloroform in the commercial preparations The irradiated vaccine protected mice against 10 000 lethal doses and the chloroformized vaccine against 1 000 the phenolized vaccine gave no protection

2 An intramuscular test designed for vaccines with too slight immunizing potency for detection by the intracerebral method simulates natural conditions and permits critical testing of canine vaccines With this a single 0 1 cc injection of irradiated vaccine was ample to immunize mice consistently against street virus

3 A third test was that of infection with virus followed by treatment with vaccine Groups of mice were given 0 01 cc street virus in dilutions into the gastrocnemius muscle and vaccine injections were commenced three hours later Nonvaccinated mice showed incubation periods exceeding 14 days and numerous survivors No phenolized vaccine has given definite protection chloroformized vaccines occasionally show some protection The irradiated vaccine however, in five doses totaling 0 5 cc prevents rabies in most instances

4 Final experiments dealt with the immunizing effects of irradiated vaccine in dogs For three years young beagle dogs had been tested for resistance to rabies by injecting early passage street virus into neck muscles Of 162 unvaccinated dogs given virus injections about 84 per cent died Of 62 dogs given commercial phenolized vaccine three weeks prior to virus injection, 72 per cent died Of 52 given chloroformized vaccine 50 per cent died Of 35 given 30-40 cc irradiated vaccine in a single dose all but 1 were protected of 24 given 5 10 cc vaccine concentrated six times all were protected

The experiments showed that the irradiated rabies vaccine is superior to commercial vaccines now available for immunizing mice and dogs against rabies It can be prepared within seven days released within another seven days is mostly free from brain tissue an [illegible]

Diseases of the Chest
(EXCEPTING THE HEART)

J BURNS AMBERSON JR M.D

PART II

DISEASES OF THE CHEST

The following articles from the literature are presented as ex amples of recent progress in the field of hest d seases and of the experience with new and old methods of diagnosis and treatment Limitations of space prohibit including many excellent and in structive articles In making selections the interest of the prac ticing physician principally has been kept in mind Articles de scribing research having only a remote bearing on cl nical prac tice have not been included but this has no relat on to their im portance and value The aim of the editor has been to select samples of work relating to various types of chest disease Many of the original articles should be consulted by those who have an interest in learning the deta ls of the work described.—Ed

ANATOMY AND PHYSIOLOGY NORMAL AND ABNORMAL—PRACTICAL APPLICATION

Malformations of the Lung G E Gruenfeld and S H Gray[1] (St Louis) state that realization that the genesis of the lungs follows the pattern of a tubular acinous duct system is essential for understanding of most instances of congenital abnormality Teratogen esis may happen at any stage of the branching out of the primitive respiratory tract and its successor the bronchial tree

Absence of Both Lungs —A case of this kind was re ported by Schmidt in an 8 month premature infant with larynx well developed and trachea not yet sepa rated from the esophageal wall but possessing several islands of cartilage The normally proportioned thor acic cavity contained only the heart with no vestiges of pulmonary veins The pulmonary artery connected as a large ductus Bottali with the descending aorta Pleural membranes were not found the diaphragm was high The arrest of bronchial development evidently

(1) A h P th 31 39 -407 Ma h 1941

took place before the primitive respiratory tube separated from the esophagus A similar case was observed by Saito but in that instance separation of the trachea from the esophagus *had already occurred*

Agenesis of One Lung—This has been reported in 36 instances Three subjects were stillborn, 5 lived less than 1 week 12 lived less than 6 months 1 lived 2 years and another 5 years and 14 lived 5 72 years The stem bronchus of the aplastic lung varied from rudimentary to full length and occasionally a nub at its end represented the agenetic lung Most authors assumed an inherent deficiency of the lung anlage as the cause of the malformation The fact that in several instances no interlobar fissure formed in the opposite lung seems to support this view

Anomalies in Branchings of the Stem Bronchi—The interdependence between lobe formation and the earliest branching of the stem bronchus is well illustrated by a typical anomaly If the eparterial bronchus fails to develop its place is usually taken by a branch developing later from the first ventral main bronchus of the right lung The upper and middle lobes may be fused Conversely an apical bronchus in the left lung directly connecting with the stem bronchus repeating the eparterial bronchus formation characteristic for the right lung is frequently associated with a trilobed left lung

Cystic Disease and So Called Congenital Bronchiectasis—It is becoming increasingly questionable whether *this deformity is always teratogenic or even congenital* The following conclusions are advanced concerning the status of cystic disease of the lung among pulmonary malformations Cystic lungs are of comparatively frequent occurrence—so frequent as to cast doubt on the probability that they are always primary malformations A convenient classification distinguishes between the multiple small cysts, i e honeycomb lung and the large cysts few in number i e pneumatoceles In

many cases the cysts are dilated branches of the bronchial tree Difficulty might be encountered in differentiating lung cysts from bronchiectases produced by scarring or obstruction Lung cysts might be produced by unknown teratogenetic factors and by a variety of pre and postnatally acquired disease processes The malformation is therefore not always primary In rare instances cystic pulmonary tissue is neoplastic

Azygos Lobe—The formation of this seemingly excessive structure is the result of mechanical interference with development of the upper lobe It does not form spontaneously but is split off from the mesial aspect of the right upper lobe by the azygos vein if and when this vessel curves in too lateral a direction from the prevertebral region to the anterior mediastinum in order to connect with the superior vena cava Since the vein is extrapleural its curving through the chest cavity necessitates the lifting off of a fold of pleura from the posterolateral thoracic wall This fold is called mesoazygos The lobe therefore is not a supernumerary structure but a part of the upper lobe

Supernumerary Lobes—Among the more typical excess formations can be counted a left apical lobe if its development can be explained by the occurrence of an anomalous eparterial branch of the left stem bronchus At the base of the lung an excess lobe is sometimes formed at the mesial aspect Such a lobe represents a segment of the lower lobe which normally is drained by a bronchus of a larger lumen and of typical course and connection the infracardiac bronchus

Supernumerary and Accessory Lungs—There are two different types of congenital anomalies A lobe in the right apical region connected by an anomalous tracheal bronchus with the tracheobronchial tree is extremely rare More often the so-called accessory lung is a mass of pulmonary tissue at the base of a lung occasionally below the diaphragm lacking bronchial connections with the lungs In either instance

the term lung is misapplied if the more plausible theories of the origin of the anomaly are credited If that part of the respiratory tract that contains a stem bronchus in its entirety is defined as a lung both modalities of *excessive or abnormally segregated lung* tissue can be considered at best as lobes and in the case of lower accessory lung only as parts of a lobe On the other hand two instances of lung anomalies unmistakably due to a displaced anlagen of a stem bronchus or even a displaced bifurcation have been reported For them the term lung is appropriate and the authors propose to call them ectopic lungs

Physiology and Anatomy of the Respiratory System in the Fetus and New Born Infant are discussed by William F Windle* (Northwestern Univ) The placenta is the organ for respiration of the fetus A stream of well oxygenated maternal blood enters the placenta *and comes into intimate contact with the fetal blood* stream, poor in oxygen The umbilical vein blood has been found highly saturated with oxygen in sheep, and there are reasons to believe that the same is true of other animals According to Mossman the fetal and maternal capillaries within the placenta do not course parallel to one another but run in opposite directions Thus the fetal blood can become equilibrated with that of the arterial end of the maternal capillary bed Although the oxygen capacity of maternal blood declines as gestation proceeds *reaching about 15 5 volumes per* cent at term, that of the fetal blood increases progressively At full term the human fetus has about 4 500 000 red corpuscles per cc but the corpuscles are large consequently it has 15 5 Gm hemoglobin per 100 cc and a hematocrit reading of 51 per cent Its oxygen capacity is 21 5 volumes per cent

In prenatal life the need for oxygen is low as compared with the condition after birth Oxygen consumption is exceedingly slight in early gestation Toward

(*) J Pediat 19 437-444 Oct ber 1941

the latter part of pregnancy the sheep fetus uses oxygen at the rate of about 0 0043 cc per Gm per minute A factor of safety exists for the total oxygen available is more than adequate to meet this need as long as normal conditions prevail in the placenta A reservoir of oxygen in combination with hemoglobin is constantly present to provide for minor variations in oxygen utilization Occlusion of the umbilical cord results in a rapid loss of oxygen from the fetal oxyhemoglobin The heart slows to conserve the store of oxygen but the fetal survival time is prolonged far beyond the point at which the blood oxygen is gone The fetus goes into oxygen debt and apparently uses its blood sugar anaerobically with the production of lactic acid thus prolonging its survival time

The physiology of respiration in utero is not so greatly different as it may seem from that of the newborn infant or even of the adult Early in embryonic life the part of the somatic motor system which is to be concerned with breathing later has its genesis Soon higher neurons are formed and are brought into a mutually integrated aggregate to comprise a respiratory center connected with the somatic motor system Appropriate stimulation by afferent nervous discharge into the center by the chemical agent carbon dioxide acting on it directly or by anoxial elevation of its excitability can bring it into premature activity It is doubtful if this newly formed respiratory mechanism actually functions in the strictly normal course of intrauterine existence The respiratory mechanism of the fetus seems to be a dormant system charged with potentialities long in advance of the time it can be of any use to the fetus Premature birth finds the new individual well prepared in respect to the respiratory system

Under experimental conditions it is easy to alter the physiologic state of the fetus in utero and to start respiratory movements In experiments with guinea pigs

and cats near the end of gestation, two types of fetal respiratory movements have been observed During mild anoxemia and in decerebrate animals after ether anesthesia, rapid rhythms of shallow movements are seen These occur with little or no increase in fetal muscle tone Practically no expansion of the fetal chest can be discerned After prolonged interference with the placental exchange mechanism and during profound anoxia the shallow rapid rhythms cease and the fetus begins to gasp rhythmically at rates of 2 to 10 per minute the muscle tonus is then increased greatly and the fetal chest expands strongly Aspiration of amniotic contents has been encountered experimentally only under conditions of anoxemia and asphyxia

Respiration begins at birth because the excitability of the respiratory center increases as anoxemia builds up *during placental separation The heightened blood* carbon dioxide and the afferent stimuli from the changed environment are important factors If the excitability of the respiratory center is unimpaired by narcotics and anesthetics breathing begins at once Rhythms of shallow rapid respiratory movements which are occasionally seen in late gestation signify that the fetus is momentarily experiencing an elevation of excitability of its center or an elevation of blood carbon going to the brain A physiologic partial anoxemia may occur toward the end of gestation as the result of progressive decline of placental efficiency with this minor rhythms of fetal respiratory movements *such as described by Ahlfeld, may be encountered However these are rare* and when observed should give cause for apprehension for they are signs of anoxemia and may warn of impending danger of fetal asphyxia That intra uterine respirations are uncommon depends on the fact that the fetal blood is well saturated with oxygen and that the fetal heart is so constructed that the most highly oxygenated blood is shunted directly to the brain, so that anoxia of the respiratory center is avoided

Effect of Lateral Body Position on Pulmonary Rest was investigated by Raul F Vaccarezza Alfredo Lanari Alvaro E Bence and Francisco Labourt[3] (Buenos Aires) Spirometric studies were made on each lung separately using the Gebauer catheter The subjects were 10 men aged 22 53 6 were healthy or had minor ailments not affecting pulmonary function 1 had tuberculosis of both upper pulmonary fields and 1 bilateral apical emphysema In addition to spirometric studies inspiratory and expiratory volumetric variations of the lungs accompanying the various postural changes were determined by corresponding diagraphs

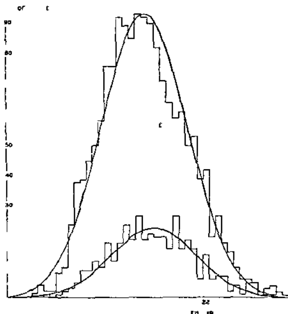
The combined function of both lungs showed no significant variations related to postural changes *The right lung* revealed greater oxygen consumption respiratory volume per minute vital capacity and complementary air in homolateral than in contralateral position The values obtained were about equal in right lateral and supine positions Reserve air gave maximum values in *left lateral position and minimum values in right* lateral position The respiratory equivalent showed no significant changes *The left lung* showed greater oxygen consumption respiratory volume per minute vital capacity and complementary air in homolateral than in supine and right lateral positions Reserve air was greater in right lateral than in left lateral position and the respiratory equivalent showed optimal values in homolateral position In general the functional capacity of the right lung exceeded that of the left lung in all positions as regards oxygen consumption (55 5 as against 44 4 per cent) respiratory volume per minute (55 6 and 44 3 per cent) vital capacity (55 9 and 44 per cent) and reserve air (58 6 and 41 3 per cent) Regarding complementary air and respiratory equivalent the right lung predominated in right lateral and supine positions but not in left lateral position Study of the diagraphs disclosed a distinct reduction in lateral

(3) Méd Mé o pp 79 93 Ap il 194

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were excluded they conclude that the association of respiration with surface area is fairly good that the correlations between ventilation and heat production oxygen consumption and carbon dioxide production are excellent and that of these the correlation with carbon dioxide production is the best



F g 1—C b n d xd ten n n xp ed a r n 2 0 1 bje t w th n k wn b rm l ty l l t d n rml rv p mpo ed

Average normal values of carbon dioxide tension and the variation with sex and age were studied in 2 021 consecutive basal metabolism determinations from which persons with respiratory abnormalities hypo and hyper thyroidism were excluded The frequency distribution of the concentration of carbon dioxide in the expired air showed a curve of the gaussian or normal type

position of both expiratory and inspiratory volumes of the lower *lung* as compared with those of the upper lung despite respiratory mobilization of the mediastinum and *the* greater respiratory excursion of *the* homolateral hemidiaphragm

The results indicate that in lateral body position pulmonary ventilation is increased in the lower lung and decreased in the upper lung The effect of the left lateral position is more marked than that of the right lateral position At first glance the greater ventilation of the lower lung suggests greater work on its part This is however, not the case From a phthisiotherapeutic viewpoint, elastic hypotension is considered the principal factor in pulmonary rest Functional rest must be differentiated from physical or elastic rest for the two often show opposite results, as seen in the present study The lower lung is better ventilated but since its *inspiratory* and expiratory volume are reduced, its elastic rest is greater The lesser expansion of the lower *lung* has been demonstrated not only by thoracometric and diagraphic examinations but also by reduction of its reserve air consequently of its residual air Hence *the* lateral position affords greater rest for the homolateral lung despite *its* increased respiratory ventilation

[This work lends objective proof to the clinical conception that lying in the lateral position rests the inflamed homolateral lung and consequently may favor healing In a study of changes in lung volume with the subject in the Trendelenburg position Altschuel and Zamcheck (*Surgery Gynecology and Obstetrics* 74 1061 1064 June, 1942) show that in this position the functional residual air is decreased suggesting changes in intrapleural pressure which make respiration more difficult and impair return of venous blood to the heart —Ed.]

Concentration of Carbon Dioxide in Expired Air was studied by Paul K. Boyer and Cameron V Bailey[4] (Columbia Univ) From *data* obtained in 500 consecutive basal metabolism determinations from which subjects with any known cause of respiratory abnormality

(4) Arch Int Med. 69 773 788 May 194

Corwin Hinshaw (Mayo Clinic) made roentgenographic studies of the effects of increased or decreased barometric pressure on pneumothorax within a low pressure chamber There was considerable variation among patients A few were found whose pneumothorax did not expand to the degree anticipated by application of Boyle s law In these instances it was possible to explain the failure of expansion on the basis of thickened pleura adhesions small capacity or other mechanical factors In one patient an extensive basal pneumothorax was established and he was receiving frequent large refills under positive pressure with production of a posterior basal mediastinal hernia dyspnea and thoracic discomfort The pneumothorax cavity was reduced approximately to half its former size with consequent reexpansion of the lung and relief of dyspnea as long as the external pressure was maintained at twice that of sea level

In three cases the external pressure was reduced to simulate *the effect of altitude of 8 000 to 12 000 ft* Two of the subjects had previously experienced discomfort during flight and these symptoms were reproduced during the experimental procedure In another instance the patient has flown frequently and it was suspected that the pleural effusion resulted from the frequent rapid and decided changes in the degree of collapse The degree of collapse reproduced in the low pressure chamber was similar to that which would be anticipated by application of Boyle s law

The evidence accumulated seems adequate to justify warning all patients with pneumothorax to avoid transportation by airplane unless they can be assured that no altitude will be attained beyond that which they have previously tolerated without discomfort Even then some harm might be done to unstable tuberculous lesions by alternate expansion and collapse which may repeatedly occur during a flight especially with frequent landings

(5) J A M A 118 1 75 1 78 Ap 11 194

(Fig 1) The mean value for females was 20 01 mm Hg and for males 20 33 mm Hg With great variation in age there was relatively little variation in the average partial pressure of carbon dioxide in expired air In both sexes ventilation tends to increase slightly with advanced age During the years of menstruation women consistently show a slightly greater ventilation proportionate to carbon dioxide production The percentage variation between sexes is small, at most about 4 per cent A study of the variability of tension of carbon dioxide in expired air disclosed that when both sexes are included the normal range limits are 18 22 50 mm Hg In experiments on hyperventilation while other factors in the respiratory exchange were varied from 36 to 168 per cent the pressure of carbon dioxide in the expired air was changed only 8 5 per cent The striking constancy of the concentration of carbon dioxide is probably dependent on the facts that ventilation closely follows the production of carbon dioxide and that even when ventilation is temporarily excessive elimination still tends to parallel ventilation because of the readily available reserve of carbon dioxide

Clinically the concentrations of carbon dioxide in the expired air and the alveolar air should both be regarded as measures of respiration When respiration is unduly stimulated both concentrations may be expected to fall When respiration is depressed both may be expected to rise Low concentrations of carbon dioxide in the expired air may be expected in persons with circulatory failure severe anemia acidosis and certain types of pulmonary disease Respiratory depression and high concentrations of carbon dioxide in the expired air will occur in persons with 'alkalosis and depression of the respiratory center such as is caused by sleep and drugs like morphine and the barbiturates

Dangers of Aerial Transportation to Persons with Pneumothorax W Randolph Lovelace II and H

ventilation equivalent was lower than in the former group and the vital capacity was practically normal

In the fourth group were 11 patients who had undergone thoracoplasty and did not show active disease on the operated side There was a moderately decreased percentage of oxygen intake on this side a high ventilation equivalent and a vital capacity disproportionately large in comparison with the oxygen intake These lungs contributed their approximately normal share to total ventilation but tidal air constituted 31 per cent of the vital capacity

In the fifth group were 14 patients with reexpanded pneumothorax lungs which contributed 12 91 per cent to the total oxygen intake indicating that some of these lungs not only may function well but may be capable of considerable compensatory overfunction

The practical conclusion from these observations is that determinations of vital capacity without additional functional tests are totally misleading Since the x ray appearance is frequently not a reliable indicator of the functional capacity of a lung bronchospirographic determinations are essential before deciding on irreversible collapse procedures particularly if the lung has been under pneumothorax treatment The functional restrictions produced by thoracoplasty are more correctly predictable than those of pneumothorax

Studies of Individual Lung Function Open Circuit Procedure with Air and Low Oxygen Mixtures as the Inspired Gases is described by Walter K Whitehead E J O Brien and William M Tuttle[7] (Detroit) It has been pointed out elsewhere that the adaptive mechanisms initiated by breathing low oxygen mixtures are either deficient or ineffective in abnormal lungs and that latent abnormalities may thus be brought to light in the resting subject In persons with abnormal lungs the arterial oxygen saturation is lower while breathing a low oxygen mixture than it is in normal subjects indicating

(7) J Th S g 11 266 77 F bru ry 1942

Traumatic and spontaneous pneumothorax present similar hazards to those of the artificial pneumothorax

Bronchospirography Max Pinner, George Leiner (New York City) and William A Zavod[6] (Mount Vernon N Y) present bronchospirographic data obtained in a few classified groups of patients

The first group comprised 31 patients with pulmonary tuberculosis potential candidates for medical or surgical collapse who had roentgen evidence of a good contralateral lung That a number of these lungs were not normal functionally was shown by the large share that they had in the total oxygen intake When all left lungs with a percentage of total oxygen intake over 60 and right lungs with a percentage over 70 were excluded there were only a few lungs left which could be considered approximately normal In these few lungs the tidal air was on the average 16 per cent of the vital capacity which is close to spirometrically normal values

In the second group were 19 patients with severely damaged lungs who absorbed in one lung only 25 per cent or less of the total oxygen intake half of them absorbed only 15 per cent Oxygen intake (respiration) was more impaired than vital capacity the ventilation equivalent was high and there was a tendency for these lungs to be in relative expiratory position as indicated by the values for reserve and complementary air Tidal air constituted a large percentage (38) of the vital capacity From the clinical data it was apparent that the outstanding factor responsible for this poor function was the condition of the pleura Each of the patients had pneumothorax followed by fibrothorax pleural obliteration unsuccessful pneumothorax attempts or pleuritis Three had phrenicectomy and the paralysis of the diaphragm contributed considerably to poor function

In the third group were 11 patients whose one lung showed parenchymal lesions but no pleural involvement The main oxygen consumption was 42 (nearly normal)

(6) J Th ac c S g 11 341 6 F br ary 194

(Trudeau N Y) and Warriner Woodruff[8] (Saranac Lake N Y) This procedure does not actually simulate collapse therapy except in that it causes increase in volume of oxygen which passes the membranes of the contralateral lung and hence might be used as a method of testing its ability to perform the task The 34 patients selected for this study had been accepted on a clinical basis for collapse therapy None had extensive damage in the contralateral lung

The investigation revealed that when one lung breathes room air and the other pure nitrogen there is an increase in the amount of oxygen picked up by the side respiring air and in most instances there is also an increase in ventilation No correlation exists between the condition of the lung tested and the ventilation response nor a close correlation between the percentage of oxygen block and the ventilation response When more than 40 per cent is blocked there is a greater increase in ventilation but there is still a wide variation in the amount of increase at all levels The most likely explanation of this variability of ventilation response is that it is due to the natural variation in sensitivity of the nerve centers controlling ventilation and to the depressant action of the narcotics on the same centers Although the diseased lung shows less ability to increase its oxygen absorption than the normal one the difference is not as striking as was expected

[Close clinical and fluoroscopic studies of the motions of the thorax and its contents enable one to estimate reasonably closely what part each lung shares in the ventilative function but such observations of course do not indicate the efficiency of gas exchange between the alveoli and the blood —Ed]

Physical and Chemical Properties of Sputum Factors Determining Variations in Portions from Different Parts of the Tracheobronchial Tree Felix P Basch Paul Holinger and Henry G Poncher[9] (Univ of Illinois) studied sputums derived chiefly from patients with

(8) J Th S g 11 8 87 F b y 1942
(9) Am J D Ch ld f 981 990 N ie 1941

that absorption of oxygen under stress is limited by the condition of the lung This principle has been applied to the study of individual lung function A low oxygen mixture is inspired first by one lung and then the other with the opposite lung breathing air In this manner one lung at a time is subjected to stress and the response of both lungs is measured simultaneously

Since it is hard to keep the composition of the breathing mixtures constant in small closed circuit spirometers containing low oxygen mixtures it was found convenient to use an open circuit method in which the inspired air is separated from the expired air without rebreathing The inspired air can be composed of any mixture of gases and its composition is constant throughout each period of observation The expired air of each lung is collected in a suitable container its volume measured and samples taken for analysis In addition to data obtainable by closed circuit spirometry carbon dioxide excretion and the respiratory quotient of the expired air of each lung can be determined The only disadvantage is the necessity for gas analysis and the longer time (5-7 minutes) needed for each period of observation Three illustrative cases are presented

The method permits quantitative estimation of three practical factors (1) performance of each lung at rest without benefit of breathing atmospheres unusually rich in oxygen (2) response of each lung to an artificial stress including the ability of the contralateral lung to compensate for a loss of function on the part of the other lung and (3) relation between circulation and ventilation in the individual lungs both at rest and under stress Such data will help not only to avoid operating on patients who would be made worse by the procedure but also to extend the benefits of thoracoplasty to some of those thought unfit

Ventilation and Oxygen Absorption of Normal and Diseased Lungs during Nitrogen Respiration in the Opposite Lung were studied by George W Wright

the pressure of secretions to form the second portion

Further observations regarding the differences between thick and thin sputum were made on the material obtained by bronchoscopic suction from two patients with postoperative massive collapse of the lungs These patients received no treatment other than bronchoscopic suction The sputum became thinner during the course of the disease and became liquefied in the later stages probably owing to bacterial action This material is characterized by a markedly higher dried residue and amount of ash than immediately after onset of the disease

Sputum of different viscosities is formed by reactive processes within the bronchi Changes resulting in a dilution may occur by the secretion of liquid substances into the sputum by resorption of solid substances or by bacterial or enzymatic liquefaction Probably all of these mechanisms are responsible for the changes which occur during the dilution of the third portion as it advances to become the second portion On the other hand the mechanism for the formation of the plug is probably principally one of drying Thus the lowering of viscosity of the sputum is not always followed by a lowering of its content of organic and inorganic material

[In another study these investigators describe the influence of drugs steam carbon dioxide and oxygen on the production of sputum concluding that inhalation of steam liquefies the sputum more efficiently than do the expectorant drugs Inhalation of carbon dioxide has a similar effect and the combination of inhalations of carbon dioxide and steam and the administration of expectorant drugs is most effective Oxygen was found to be an antiexpectorant and in this class are included also codeine sulfate and atropine sulfate (*American Journal Diseases of Childhood* 6 1149 11 1 December 1941) See also Holinger Basch and Porcher this YEAR BOOK p 165—Ed]

bronchiectasis principally children Frequent bronchoscopic aspirations provided an accurate method for obtaining material for study and a constant check on the material coughed up

Sputum may be divided both physically and chemically into three types, which must not be confused with the classic three layers into which the sputum of patients with abscesses of the lung or bronchiectasis separates on standing The first and second portions obtained by postural drainage could be distinctly separated The first portion was found to be a bronchial mucous plug never measuring more than 5 10 cc regardless of the total amount of sputum coughed up It was extremely thick and viscid but the amount of ash and the total nitrogen content were lower than in the subsequent portions Sputum which is raised by ordinary cough and during postural drainage has been designated as the second portion It is the largest in volume of the total sputum content of the trachea and bronchi and is identical with that first aspirated when a bronchoscope is inserted into the trachea of a patient with copious sputum It usually has a relatively high dried residue and a constantly high percentage of ash The amount of total nitrogen was irregular The viscosity of this portion was definitely and constantly lower than that of other portions The sputum constituting the third portion is found in the most dependent parts of the bronchial tree and remains after the most vigorous postural drainage has cleared the trachea and the larger bronchi of their content It may be obtained only by bronchoscopic suction It is characterized by a relatively high dried residue and percentage of ash Its most characteristic property however is its extremely high viscosity which becomes even higher when the sputum is removed from the bronchi by aspiration and allowed to stand Sputum raised spontaneously by cough does not have this property The third portion is moved to a higher level in the bronchi both by the tussive squeeze and by

the pressure of secretions to form the second portion

Further observations regarding the differences between thick and thin sputum were made on the material obtained by bronchoscopic suction from two patients with postoperative massive collapse of the lungs. These patients received no treatment other than bronchoscopic suction. The sputum became thinner during the course of the disease and became liquefied in the later stages probably owing to bacterial action. This material is characterized by a markedly higher dried residue and amount of ash than immediately after onset of the disease.

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[In another study these investigators describe the influence of drugs, steam, carbon dioxide and oxygen on the production of sputum, concluding that inhalation of steam liquefies the sputum more efficiently than do the expectorant drugs. Inhalation of carbon dioxide has a similar effect, and the combination of inhalations of carbon dioxide and steam and the administration of expectorant drugs is most effective. Oxygen was found to be an anti-expectorant, and in this list are included also codeine sulfate and atropine sulfate (*American Journal of Diseases of Childhood* 66: 1142 11 1 December 1943). See also Holinger, Basch and Poncher, this YEAR BOOK, p. 16?.—Ed.]

A Method for Studying Expectorant Action in Animals by Direct Measurement of the Output of the Respiratory Tract Fluids is presented by William F Perry and Eldon M Boyd[1] (Queen's Univ) Cats and rabbits were anesthetized with ethyl carbamate a side arm cannula was inserted into the trachea the animals were arranged head down on a board and the inspired air was warmed to body temperature and saturated with water vapor The respiratory tract fluid was allowed to drain into a measuring tube and the exposed parts were insulated to prevent condensation of vapor Under these conditions the absolute output of the respiratory tract fluid differs somewhat from that of a normal animal but the relative effects of the various factors and of expectorant drugs should correspond to those in normal animals

The mean rate of production of fluid equaled about 2 cc per kg per 24 hours in both rabbits and cats corresponding to a total daily output of 5 cc for an adult animal The output during the second hour of experiment could be taken as an approximation of the control value and if any drug administered at the end of the second hour affected the subsequent hourly output by 50 per cent or more it could be considered to have a significant effect The fluid consisted of an opaque yellowish mucus-like liquid containing some white and red cells and epithelial cells The precipitate gave a positive reaction to the Benedict test for sugar after acid hydrolysis and was insoluble in excess acetic acid indicating that it contained a mucin The mean viscosity of the clear mother liquor was 1 36 in rabbits and 1 2 in cats the density in both 1 1 1 It gave qualitative tests for chlorides, sodium potassium calcium and protein and the ashes yielded minute amounts of iodine Tem

(1) J Pharmacol & Exper Therap 47 65 77 September 1941

perature and humidity of the inspired air markedly affected the output of fluid When air at 21 to 22 C and 10 to 20 relative humidity was inspired the rate of output fell to about 5 per cent of that in animals inspiring air at 35 to 38 C and 80 to 90 per cent relative humidity Smaller animals produced fluid at a rate faster than that of larger animals The absolute output decreased during winter months

A dose of 0 4 Gm ammonium chloride per Kg given by a stomach tube appreciably increased the output The mean rate two hours after the drug was given was 88 per cent greater than that during the control period (one hour before the drug was given) the secretion was more viscous and contained more mucus and less chloride sodium and potassium The facts that the drug given intravenously had a lesser effect than when given by stomach tube and that it did not increase the output when given by mouth to animals with the gastric nerves severed indicated that it exerts a reflex expectorant action from the stomach Ammonium carbonate in doses of 0 5 Gm per Kg body weight given by stomach tube increased the mean output by 110 per cent within one hour Powdered ipecac B P suspended in saline given in a dose of 1 Gm per Kg by stomach tube increased the output of respiratory tract fluid by 43 per cent in rabbits and by 143 per cent in cats Glycerol guaiacolate (resyl) in doses of 0 01 Gm and pilocarpine nitrate in doses of 8 5 mg per Kg both injected intraperitoneally likewise increased the output Stimulation of the vagus nerve increased the output in both rabbits and cats

[Such studies as these are welcome since they provide a mu [ore sound rationale for the use of expecto ant drugs —Ed]

The Influence of Expectorants and Gases on Sputum and Mucous Membranes of the Tracheobronchial Tree was investigated by Paul Holinger Felix P Basch and Henry Poncher[2] (Univ of Illinois) In general the factors responsible for liquefying sputum within the

(2) J A M A 117 675 678 A g 30 1941

bronchi thus aiding in its evacuation, consist of those agents which will increase the hyperemia of the mucosa and those which will increase the depth and rate of respiration The action of expectorant drugs is almost uniformly favorable in liquefying a portion of the sputum which lies in the first and second division bronchi but rarely affects the dependent viscid secretions in the peripheral bronchi The actions of gas inhalations are quite specific and they grossly influence the physical and chemical qualities of both expectorated and bronchoscopically obtainable sputum and the character of the bronchial mucosa Steam inhalation or inhalation of a high humidity atmosphere, results in liquefaction of sputum Carbon dioxide may be considered as an extremely efficient expectorant It alone reaches the deeper, obstructive type of secretion which must be frequently and efficiently drained to prevent serious types of permanent pulmonary or bronchial damage It is apparent that the action of carbon dioxide is partly dependent on its ability to stimulate an actual resorption of secretions However its most important actions are to enforce deeper more active respiratory movements to liquefy the sputum and to stimulate the cough reflex By evacuating the more dependent bronchi, sputum otherwise inert is brought to a level from which it can be coughed out easily or removed more efficiently by direct suction through the bronchoscope In addition to lowering the viscosity of the sputum carbon dioxide also reduces its organic and inorganic content Its effect on the bronchial mucosa consists in producing a definite hyperemia in the involved parts of the lung

Administration of oxygen results in increase of viscosity of the sputum and in increase in its content of organic and inorganic substances The bronchoscopic picture shows the tracheobronchial mucosa to be pale or even blanched with plaques of mucus adhering to the bronchial wall Oxygen acts thus specifically as an antiexpectorant therefore its use alone is contraindi

cated in obstructive lesions whose obstruction is in part at least due to copious viscid secretions This deleterious effect may be neutralized partially or wholly by addition of steam and 5-10 per cent carbon dioxide In this manner not only the tremendous value of oxygen in alleviating the symptoms of respiratory embarrassment or even respiratory decompensation is retained but also necessary aid in removing the obstruction is given The use of codeine and atropine at regular intervals over a long time is contraindicated in bronchopulmonary suppuration producing obstructive symptoms however use of atropine prior to bronchoscopy may be justified in reducing the total amount of secretion and thus making the procedure easier for the patient

Use of the various agents described may be of distinct advantage in the treatment of certain diseases In bronchiectasis and certain types of asthma in which bronchial obstruction plays a role frequent inhalations of carbon dioxide by mask together with steam inhalations may be used to increase the postural drainage and bronchoscopic aspiration which are fundamentally important Use of steam and carbon dioxide between bronchoscopies and especially shortly prior to bronchoscopy is indicated if the sputum is known to be extremely thick and tenacious This also enhances the action of the expectorant drugs administered In laryngotracheobronchitis in which the obstructive element is not alone the inflammatory edema but the secretions and products of inflammation which adhere to the laryngeal and bronchial surfaces the use of a room at 70 to 75 F with a relative humidity of 80 to 95 per cent provides satisfactory conditions for liquefying secretions If because of an increasing edema obstruction of the airway progresses despite removal of secretions oxygen may become necessary In such instances adequate provision for a high degree of humidity in the oxygen tent is essential and is best accomplished by the attachment of a mechanical humidifier to the tent

Postoperative massive collapse of the lung, produced by occlusion of a major bronchus by viscid mucopus is almost always spontaneously relieved if the patient can be induced to breathe deeply and cough Steam inhalations aid in liquefying secretions and thus facilitate their removal, but carbon dioxide has become the most commonly used expectorant in treatment of this disease because of its extremely efficient action in increasing the rate and depth of respiration as well as in aiding to liquefy the secretions Actual bronchoscopic suction when these agents fail or if the condition of the patient demands immediate intervention must always be available

[Tuft and Lebin (*American Journal of the Medical Sciences* 205 717 722 May 1943) demonstrated that in the human iodides given orally or intravenously are excreted in the bronchial secretions within 15 to 25 minutes They concluded that this excretion probably accounts for the expectorant action and that oral administration is as effective as intravenous —Ed]

Effect of Intravenous Theophylline with *Ethylene* Diamine (Aminophylline) on Rate and Depth of Respiration Louis Sperling Sydney Weisman and Ralph Papermaster[3] (Univ of Minnesota) studied patients in surgical wards awaiting operation and during immediate postoperative convalescence The depth of respiration was measured in centimeters of needle excursion on the kymograph of the basal metabolism apparatus and the figures obtained were transposed into cubic *centimeters for volume of air inspired* Blood pressure and pulse rate were recorded prior to injection and at intervals of 2 and 10 minutes after injection

Aminophylline was given intravenously in *0 48 Gm* doses to 22 patients with no evidence of pulmonary involvement and to 3 with postoperative atelectasis In the 22 normal patients there were a maximum *imme*diate increase in rate averaging 26 per cent and an immediate increase in depth of respiration averaging 51 per cent All showed an increase either *rate or depth*

(3) Surg 11 600 604 Apr il 1942

or both during the injection or immediately afterward In one case the increase in rate persisted over 3) min utes There was no significant increase in pulse rate None of the patients complained of subjective ill effects In the three patients with atelectasis administration of 0 48 Gm aminophylline at four hour intervals was followed by disappearance of the rhonchi and the symp toms incident to bronchial obstruction However other

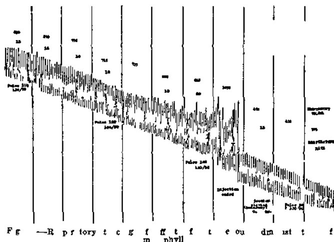


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measures such as encouraging the cough reflex steam inhalation and postural drainage were likewise used

Coramine in doses of 1 5 and 2 cc intravenously was given eight patients in a second series There was comparatively slight increase in rate and depth of respiration and no significant effect on blood pressure or pulse rate in patients without evidence of respira tory or cardiac depression Three control patients given saline solution intravenously showed no significant changes in rate or depth of respiration

Aminophylline was given routinely to 69 patients undergoing abdominal operation at the University Hos

pital and to over 100 similar private patients Only three in both groups developed respiratory complications.

THE PNEUMONIAS

In this country there is now a strong tendency to favor sulfadiazine for the treatment of most pneumonias although the following articles describe work substantiating the efficacy of other sulfonamides also In England sulfadiazine has not been readily available and objections have been raised to its use because of its cost Recently a new derivative sulfamethazine was described by the English workers Macartney, Luxton Smith Ramsay and Goldman from Crumpsall Hospital Manchester (*Lancet* 242 639-641 May 30 1942) Their clinical trial suggests that its therapeutic efficiency is high and that it is highly soluble and hence unlikely *to cause renal damage The last is one of the objections to some* of the other sulfonamide compounds Another sulfonamide derivative irgamid is described by the Swiss Markoff (*Schweizerische Medizinische Wochenschrift* 72 334 340 Mar 21 1942) who makes claims for its efficacy and low toxicity in clinical practice —Ed

Behavior of Plasma Prothrombin in Pneumonia Leandro M Tocantins and Welland A Hause[4] (Jefferson Med College) studied 31 patients aged 11 70 Fifteen had typical and 16 atypical lobar pneumonia, nearly all of the former had sulfathiazole treatment They were generally admitted after the third day of the disease Plasma prothrombin was measured in quadruplicate by the Quick method with slight modification To an additional separate group of six patients with pneumonia and hypothrombinemia a vitamin K substitute was administered after the first prothrombin determination was obtained

In 18 patients the quantitative prothrombin was below 70 per cent of normal on admission and in 23 it was below 70 per cent at some time during illness In 16 it was below *50 per cent at some time during illness* Thirteen patients had some manifestations of bleeding such as epistaxis spitting up or vomiting blood in 10 of these prothrombin was 50 per cent or less some time during illness and in 12 it was below 70 at some time In 18 patients who had no bleeding during illness the

(4) Am J Clin Path 11 849 856 Dec 1941

prothrombin was below 70 per cent at one time and in 6 of these it was below 50 per cent Fifteen patients showed no significant fluctuations of prothrombin during illness in 13 there was a gradual rise from the low levels and in 2 the prothrombin declined In one of the last two the diminution coincided with development of complications and was followed by death No significant relationship could be demonstrated between a particular pneumonia producing organism and the occurrence of hypothrombinemia or manifestations of bleeding There was however a close correspondence between the degrees of incidence of bleeding and hypothrombinemia in each group of pneumonias arranged according to the causative organism Of the six patients who received a vitamin K substitute by mouth two responded fairly rapidly even before temperature returned to normal the other four did not respond to doses as high as 3 mg quinone by mouth daily

The hypothrombinemia and thrombopenia of pneumonia are probably largely responsible for delayed coagulability of the blood and hemorrhagic manifestations observed in the acute stage Several factors may conceivably influence the occurrence of hypothrombinemia (1) interference with synthesis of prothrombin due to impaired hepatic function (2) increased utilization of prothrombin brought about by the large amount of fibrin being laid down in the pneumonic areas during the acute stage (3) diminution in intake of vitamin K or in digestion and absorption of foods containing this vitamin a result of the inevitable impairment of nutrition during the acute stage In the presence of an active infectious process the response to vitamin K therapy is not as striking as in the hypothrombinemia found in other states

Sputum Studies in Pneumonia Selection of Therapy Arthur W Frisch and Alvin E Price[5] (Wayne Univ) report on 270 roentgenologically proved typed cases of

(5) An Int M d 15 987 993 D emb 1941

pneumonia in which the sole criteria for selection of therapy were the sputum findings and clinical data on admission Subsequent specimens of sputum were obtained at 12 hour intervals to determine whether a therapeutic effect had been obtained and appropriate treatment was instituted if the number of pneumococci per field increased Serum therapy was discontinued when clumps of pneumococci appeared

A group of 48 patients received no specific therapy None had a positive blood culture and only a few had a leukocyte count below 10 000 or more than one lobe of the lungs involved All showed 10 or less pneumococci per oil immersion field throughout their illness Specific therapy was withheld because it was thought that either adequate immunity was present or the infection was mild enough to be kept in check by the natural defenses of the patients All recovered satisfactorily

A second group of 70 patients had been ill less than four days and sputum findings suggested a relatively mild infection (10 pneumococci per field or less) Since these patients had not been ill long enough to develop active immunity they received specific serum to prevent development of a more serious pneumonia Although the bacteremic incidence in this group was 17 per cent and the average dose of serum only 35 000 units there were no deaths

Chemotherapy was reserved for the moderate and severe cases (11 50 pneumococci per field) which heretofore had responded poorly or not at all to serum In 114 patients given chemotherapy alone bacteremic incidence and multiple lobe involvement were significantly increased over those found in the previous two groups The ultimate fatality rate of only 6 per cent in the presence of 40 per cent bacteremic incidence justifies fully the choice of therapy The data also represent additional evidence for the therapeutic efficiency of sulfapyridine and sulfathiazole in moderately to severely ill patients

Patients with sputum counts exceeding 50 per field were considered as potentially overwhelmed by their infection Most of these 24 patients showed bacteremia low total leukocyte counts and two or more lobes involved during the course of their illness They were given accordingly large doses of serum in addition to chemotherapy (predominantly intravenous) Despite intensive treatment the mortality rate was 58 per cent

The remaining 14 patients were placed in a miscellaneous group because of various complicating circumstances

Cutaneous Reactions to Specific Soluble Substance in Infants and Children are discussed by Ruben Meyer and Benjamin W Carey[6] (Detroit) Forty two patients with typed pneumococcic pneumonia were studied with the Francis test The distribution according to therapy was sulfapyridine and serum 9 sulfathiazole and serum 12 sulfapyridine 9 sulfathiazole 12 When positive reactions were obtained they corresponded to those described in adults a wheal surrounded by a zone of erythema appeared in 10 to 20 minutes and disappeared in 1 to 2 hours

When specific antipneumococcus serum was given intravenously it was found that only one skin test was needed and that after this area became positive serum therapy could be discontinued The optimal dosage of serum is still in doubt After single intravenous doses were limited to 5 cc fewer serum reactions consisting of chills and temperature elevations were encountered By utilizing the Francis test less serum was given with comparable therapeutic effect The results of skin tests in patients who received chemotherapy alone were not uniform On the other hand the patients who received serum developed strong reactions which persisted throughout their hospital stay

To verify the concept that the reaction is due to a local union of antigen and antibody a normal infant received 0 1 cc specific soluble substance intradermally

(6) J P d t 19 481-484 O t b 1941

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monia were more toxic than others vomiting abdominal pain delirium and meningismus occurred more often and empyema occurred 18 times more often in this type than in the others The mortality however was not greater than in other types Many patients were dehydrated and ketotic on admission About 60 per cent had acetone in the initial specimen of urine Albuminuria occurred in 6 per cent and in 25 per cent of those with type I pneumonia Twenty six per cent of patients had leukopenia

Suppurative otitis media occurred in 53 cases (7 4 per cent) the incidence was greatest in the younger age groups The second most frequent and the most severe complication was empyema which occurred in 29 cases (4 per cent) Sputum typing was accurate in only 65 per cent of empyema cases Four of the patients with empyema died

The general mortality rate was 2 73 per cent When two children who died on readmission and nine who died within the first 24 hours were excluded the rate was 1 33 per cent All but one of those who died were under 4

Of the 731 children 656 (87 1 per cent) received sulfapyridine 19 (2 6 per cent) received serum in addition and 75 (10 2 per cent) received no specific medication having been moribund or convalescent on admission The usual dose was 1½ gr per lb body weight on the first day and ¾ 1 gr per lb on subsequent days Children over 6 received somewhat smaller doses The average amount of sulfapyridine required to reduce the temperature to normal was 3 21 Gm and the average total dose was 6 17 Gm Of unfavorable reactions referable to the drug vomiting was recorded in 17 per cent hematuria due to irritation by acetyl sulfapyridine crystals in 3 6 per cent acute cerebral manifestations in two per cent rash in a few cases and hemolytic anemia in one case No death could be attributed to chemotherapy

in one area and 12 hours later in another Neither injection produced a reaction One hour after the second inoculation, both areas as well as a third received 0 05 cc homologous serum The sites that had received specific soluble substance showed strong wheal and erythema reactions The control was entirely negative These reactions were duplicated in three other normal children

Pneumonia in Children A review of 731 cases of pneumonia in children aged 1 13 entering Cook County Hospital from April 1939 through May 1940 is presented by Craig D Butler, Noel G Shaw Samuel J Hoffman Sol Ditkowsky Emerson McVey and Mary Zeldes[7] Fifty four per cent were boys and 46 per cent girls 60 per cent were white and 40 per cent Negro Forty five per cent had bronchopneumonia and 55 per cent lobar pneumonia In the group aged 1 2 years 68 per cent had bronchopneumonia while in the group over 4 72 per cent had lobar pneumonia The greatest number of patients were admitted in March and April 1940 and the fewest in the summer of 1939 Approximately 50 per cent of deaths occurred from July to October *1939 when only 11 per cent of the patients were admitted*

In approximately 78 per cent of the cases there were pneumococci in the laryngeal swab Other organisms notably streptococci and staphylococci were identified in 17 per cent while in 5 per cent no bacteriologic diagnosis was made The four types of pneumococci most frequently recovered were I VI XIV and XIX types I, II, III, VII and XIV were found most frequently in *lobar* pneumonia while types above XX predominated in bronchopneumonia Types VI and XIX were found with equal frequency in both forms Blood cultures were positive on admission in 32 cases (4 per cent) in 17 of these there were no symptoms of bacteremia and the patients were discharged within eight days after admission Patients with type I pneumococcic pneu

(7) J A M A 117 1840 1843 N .9 1941

75 per cent and when there was bacteremia without carbohydrate the death rate was 35 per cent The death rate in patients with capsular carbohydrate without bacteremia was 60 per cent and with bacteremia and carbohydrate 56 2 per cent The detectable specific carbohydrate occurred five times more frequently in patients over 40 than in younger patients and twice as frequently after the fourth day of the disease than in those coming for treatment earlier

Specific antibodies appeared in 66 per cent of patients treated with chemotherapy Antibodies developed least frequently in type III patients and most frequently in type VII patients Antibodies were more frequently detected in patients under 40 than in those over 40 The patients over 40 who did not develop antibodies had a mortality almost four times greater than those who did develop them

In addition to the specific carbohydrate which is in the capsule of the pneumococcus there may be extracted from the bodies of decapsulated and no longer type specific pneumococci another carbohydrate which is not type specific—the C substance During the acute phase before specific immunity has developed C substance precipitates C protein from the serum of patients with pneumococcic streptococcic staphylococcic Bacillus Friedlander infections and infections due to other agents It is not present with mild bacterial infections or with febrile conditions due to organisms which usually do not produce pneumonia Of 417 adult pneumonia patients only 6 8 per cent failed to show it In 90 per cent of the patients it was present by the ninth day of the disease It disappeared in over half the patients on the tenth day Among patients with C protein the older patients those treated late and those with nonpneumococcic pneumonias had the highest mortality There were no deaths in the 27 negative C protein cases In 15 per cent of cases the C protein disappeared before the temperature fell in 85 per cent

[It is well to emphasize the tendency to recurrence and also the atypical behavior of pneumonia affecting a previously damaged lung Under these circumstances the course of the disease may be prolonged In such cases investigation should be made to ascertain the nature of the preexisting damage and if possible to remedy it —Ed]

Chemotherapy of Pneumonias and Immunity Reactions are discussed by Jesse G M Bullowa, Nathan H Shackman and Daniel Stats[8] (New York Univ) Immunity induced by pneumococci may be cellular or humoral as well as local and general The local cellular response is a multiplication of cells dilatation of capillaries migration of red blood cells leukocytes and macrophages Capsular carbohydrate of the pneumococci induces the production of type specific antibodies These antibodies precipitate capsular carbohydrate (thereby limiting edema in the lungs) and swell the pneumococcus capsules and agglutinate them and at the time of crisis by sensitizing them assist in both lysis and phagocytosis To a degree the virulence of a pneumococcus is determined by the amount and character of the capsular carbohydrate produced and its ability with pneumococci to act as antigen or induce production of antibodies In some cases the carbohydrate is detected in the blood and urine or in an infected serous cavity

The significance of detecting capsular carbohydrate in the blood was investigated The patients were being rotated for treatment with serum therapy chemotherapy and the combination Capsular carbohydrate was detected in the blood of 6 6 per cent of those receiving combined therapy It occurred most frequently in type III patients with an incidence of 13 5 per cent of patients The death rate in patients with detectable capsular carbohydrate was 58 1 per cent as compared with 12 per cent of the cases without carbohydrate When there was neither bacteremia nor capsular carbohydrate the death rate regardless of treatment was

(8) An I t Med 16 57 0 Ja u ry 194

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Specific antibodies appeared in 66 per cent of patients treated with chemotherapy Antibodies developed least *frequently in type III patients and most frequently* in type VII patients Antibodies were more frequently detected in patients under 40 than in those over 40 The patients over 40 who did not develop antibodies had a mortality almost four times greater than those who did develop them

In addition to the specific carbohydrate which is in the capsule of the pneumococcus there may be extracted from the bodies of decapsulated and no longer type specific pneumococci another carbohydrate which is not type specific—the C substance During the acute phase before specific immunity has developed C substance precipitates C protein from the serum of patients with pneumococcic streptococcic staphylococcic Bacillus Friedlander infections and infections due to other agents It is not present with mild bacterial infections or with febrile conditions due to organisms which usually do not produce pneumonia Of 417 adult pneumonia patients only 6 8 per cent failed to show it In 90 per cent of the patients it was present by the ninth day of the disease It disappeared in over half the patients on the tenth day Among patients with C protein *the older patients those treated late and those* with nonpneumococcic pneumonias had the highest mortality There were no deaths in the 27 negative C protein cases In 15 per cent of cases the C protein disappeared before the temperature fell in 85 per cent

it disappeared within three days after the temperature fell Of the 23 patients who recovered when C protein persisted beyond three days pneumonia had not re solved in 16 bronchiectasis was suspected in 1 serum sickness was present in 5 and pleural effusion in 2 The study of C protein may be of value in diagnosis and treatment when correctly interpreted Its presence in large amount indicates response to an irritant, and its disappearance after chemotherapy may indicate that a febrile episode is not due to infection or complication but to the drug

When sulfonamides are ineffective in reducing the pulse and temperature of pneumonia patients the fol lowing may be a possible explanation (1) wrong di agnosis—pneumonia not due to sulfonamide affected organism (2) *ineffective concentration due to nonab sorption* conversion rapid excretion or insufficient penetration (3) too many organisms because the dis ease was treated late (4) fastness—original or devel oped (5) antisulfonamide substances—persistence of *capsular carbohydrate and organisms in pus* (6) *toxic* action (7) failure of immunity responses

Pneumonia in a Rural Practice The incidence and mortality of pneumonia and the care of patients in a town of 435 population are reported by Edwin J Simons[9] (Swanville Minn) *in the belief that they* typify customary rural treatment of pneumonia and its results under the American system of medicine Since Oct 1, 1937, in all cases in which either symptoms or clinical signs suggested pneumonia a specimen of sputum was sent to the Minnesota *Department of* Health for typing On the basis of this sputum typing during 4½ years from October 1937 to April 1942 117 proved cases of pneumococcic pneumonia were en countered There were 70 males and 47 females a ratio of 60 40 *Ages ranged from 4 weeks to 83 years* Age incidence revealed a higher rate of pneumonia in the

(9) J A M A 119 6 0 6 3 June 20 1942

age group 0 4 years than is customarily seen Forty two per cent of the patients were children under 10 Only 19 of the patients were hospitalized x ray films confirmed the diagnosis in 18 and the other patient presented postpneumonic empyema Complications occurred in 39 cases Of these cardiac disturbances varying from auricular fibrillation to coronary occlusion and decompensation were the most frequent Empyema asthma bronchiectasis and effusion occurred in one or more cases Otitis media was not infrequent in younger patients Nephritis kidney hemorrhage and prostatic obstruction were recorded The history of symptomatology was considered positive in 100 per cent of cases Physical findings were typical or positive in only 83 per cent probably because of the high incidence of childhood cases

A comparison of the incidence of pneumonia with an analogous period in the same practice revealed only 60 cases of pneumonia in 4½ years prior to pneumococcus typing Consequently the statement seems justified that the incidence of pneumonia in rural practice is higher than its diagnosis in the past has indicated Despite frequent absence of typical or pathognomonic signs for pneumonia many cases diagnosed as influenza or bronchitis with proper bacterial study and typing should be classified as pneumococcic pneumonia

During the early part of the present study serum was given as quickly as it was received dosage varying with age length of illness type complications and severity Nineteen patients received serum alone and 1 of these died a mortality of 5 3 per cent When the sulfonamides became available 26 patients received both serum and chemotherapy and none died Forty six patients were treated with either sulfapyridine or sulfathiazole alone all recovered Both drugs were administered in the doses recommended in the literature except that the first dose was 1 Gm rather than 2-4 Gm often advised Blood levels were determined only

in some of the hospitalized cases Throughout the study period 26 patients for various reasons received neither serum nor sulfonamides, and 4 died a mortality of 15 4 per cent

The results of the use of serum and chemotherapy are reflected in a reduction of mortality from 16 25 per cent *in the 80 cases of the previous series treated symptomat*ically to 4 27 per cent in the 117 cases of the present series treated after the advent of specific therapy Comparison of the total mortality in urban and teaching centers with that in a rural series shows a mortality of 11 85 per cent in 32 352 urban cases and a mortality of 9 15 per cent in 197 rural cases These rates corrected by the deduction of 1 310 cases with 31 per cent mortality from the urban series and 80 cases with 13 deaths from the rural series in which no specific treatment was given are found to be 8 0 and 4 27 per cent respectively

Pneumonia Study of 132 Cases Treated in the Home with Sulfathiazole is reported by Joseph Rosenthal William A MacColl and Joseph A Pratt[1] (Tufts College)

Preliminary examination included history physical examination typing of sputum (in children of nose and throat swabs) complete blood counts including the differential blood culture and urinalysis Treatment was then started at once The first dose of sulfathiazole was given by the physician or in his presence The initial dose in adults was 4 Gm followed by 1 Gm every four hours day and night until the temperature had been normal for 72 hours In children the initial dose was 0 065 Gm per lb body weight followed by the same dose given daily in six equally divided parts every four hours night and day until the temperature had been normal for 36 hours The patients were to take 3 qt fluids daily consisting of coffee tea coca cola fruit juices for supply of carbohydrates and broth soup and bouillon made

(1) New England J Med 226 845 849 1942

from cubes for the supply of minerals In children a simple mixture of 3 tablespoonfuls of sugar or Karo and 1 teaspoonful of salt in 1 pt water was used to give approximately 5 per cent glucose and saline Supportive treatment consisted mainly of high caloric diets sedation for chest pain and general nursing care No oxygen digitalis or artificial stimulants were used.

In most cases treatment was instituted within 48 hours and in nine cases within 12 hours after onset of the disease Pneumococci were found in the sputum in 70 cases (53 per cent) Positive blood cultures were noted in six cases mortality among this group was 17 per cent The initial white blood cell count ranged from 2 000 to over 50 000 Leukopenia was not a contraindication to sulfathiazole therapy The average length of time before the temperature dropped to normal was about 48 hours The average total dose of sulfathiazole in typed cases was 37 Gm in adults and 12 Gm in children in nontyped cases 23 Gm in adults and 10 Gm in children The average actual duration of treatment in the home seemed to be less than for patients treated in the hospital It averaged 4 days for adults and 3 6 days for children with pneumococci in the sputum and 3 8 days for adults and 3 4 days for children who did not show pneumococci in the sputum

The outstanding toxic symptom was vomiting which occurred in 20 cases (in some probably due to the disease) Three patients had abdominal distention which might have been due to the drug Two had a skin rash one gross hematuria and a few microscopic hematuria Included among complications were one instance each of dry pleuritis empyema serous pleural effusion and diabetic acidosis and four of pertussis in infants Eleven patients had to be hospitalized In the five patients who died the associated diseases were cirrhosis of the liver chronic alcoholism congestive heart failure cerebral thrombosis and chronic congestive heart failure with tuberculosis

Treatment of Pneumococcic Pneumonia with Sulfadiazine and Sodium Sulfadiazine in 200 consecutive adults is reported by Harrison F Flippin S Brandt Rose Leon Schwartz and Albert H Domm" (Phila delphia Gen l Hosp) Sulfadiazine constituted the principal therapeutic agent in all but 21 cases in which treatment was exclusively with sodium sulfadiazine given intravenously Included in the sulfadiazine treated group were 15 seriously ill patients who received an initial intravenous injection of sodium sulfadiazine as a supplement to oral sulfadiazine Type specific serum was used in addition to sulfadiazine in 24 patients To prevent inhibition of growth of the pneumococcus by the drug sulfadiazine containing specimens of blood were cultured in a medium containing para aminobenzoic acid

Among the 200 patients there were 24 deaths (12 per cent) 8 of which occurred within 24 hours after admission The corrected mortality was 8 3 per cent Positive blood cultures were obtained in 20 5 per cent of patients with a mortality of 34 1 per cent the corrected mortality was 22 8 per cent Oral sulfadiazine yielded a mortality comparable to that of intravenous sodium sulfadiazine Twenty four patients in the whole series (11 4 per cent) had infections caused by type III pneumococcus with a mortality of 22 7 per cent This is due partly to the relatively high incidence of type III pneumonia in elderly patients with associated diseases Of the 200 patients 70 6 per cent were under 50 with a mortality of 3 3 per cent as compared with 38 8 per cent for those 50 and over Patients treated during the first four days of illness had a mortality rate of 5 9 per cent those treated after the fourth day 24 2 per cent

A critical fall in temperature occurred in 69 9 per cent of patients in 24 hours and in 84 1 per cent during the first 48 hours of treatment The temperature fell and remained within normal range in 17 6 per cent of patients in 24 hours and in 55 1 per cent in 48 hours

( ) W r Med "84 94 M ch 194"

Patients receiving sodium sulfadiazine intravenously showed a similar incidence of critical fall in temperature but regained a normal temperature at a slower rate. Massive pleural effusion necessitating therapeutic aspiration occurred in 4 per cent of the present series and empyema in 1.5 per cent with no deaths. Acute pneumococcic endocarditis occurred in three cases (1.5 per cent) and acute pneumococcic pericarditis in one case, all of which were fatal. The incidence of toxic reactions is shown in the table. It was the same with oral sulfadiazine as with intravenous sodium sulfadiazine.

INCIDENCE OF TOXIC REACTIONS AMONG 200 PATIENTS WITH PNEUMOCOCCIC PNEUMONIA TREATED WITH SULFADIAZINE

TOXIC REACTION	INCIDENCE	
Nausea and vomiting		
Mild	3.5	
Moderate	1.0	4.5
Severe		
Hematuria, microscopic	4.0	
Dermatitis	1.0	
Drug fever	1.0	
Leukopenia (white cell count below 5 000 per cu. mm.)	1.5	
Psychosis	5.0	

The dose of sulfadiazine was 3 Gm. initially, followed by 1 Gm. every six hours until the temperature remained normal for 48 hours and clinical improvement became evident. In general the total dose was 20-30 Gm., depending on such factors as the day of illness on which treatment was started, bacteremia, spread of infection and renal function. When a rapid elevation of the blood level of the drug was desired or when oral administration was impracticable, a 5 per cent solution of sodium sulfadiazine was given intravenously. An initial 3 Gm. dose was followed by 2 Gm. every 12 hours until the temperature remained normal for 48 hours and clinical improvement was evident.

In the authors' experience there is no particular blood concentration of sulfadiazine which is optimal for treatment of pneumonia. They believe that if a level of 5 mg

free drug per 100 cc is maintained, satisfactory results may be expected They conclude that because of its *therapeutic effectiveness and low toxicity sulfadiazine* is the best drug now available for treatment of pneumococcic pneumonia

Further Studies on Recurrences in Pneumococcic Pneumonia with Special Reference to the Effect of Specific Treatment are reported by Elias Strauss and Maxwell Finland[3] (Harvard Univ) The material comprises 168 patients with 191 recurrences All but one were over 13 and 37 were 50 or older at the time *of the initial attack* Forty eight of the patients were females Four patients had four recurrences each 14 had two recurrences and the remaining patients had a single recurrent attack One hundred twenty eight patients had lobar pneumonia in the initial attack and 40 had an atypical pulmonary lesion Of the recurrent attacks 132 were lobar pneumonia Nearly three fifths of the patients had lobar pneumonia in both the initial and the recurrent attack in less than 30 per cent of all *the attacks the character of the lesion was different in* the first and the subsequent attacks in the same patient There was no tendency for the recurrence to involve the lobe affected in the first attack any more than any other lobe the incidence of bilateral involvement in the early and later attacks was nearly identical Chronic pulmonary disease to which the attacks of pneumonia were thought to be secondary was present in 25 These were bronchiectasis chronic passive congestion of the lung due to cardiac disease pulmonary tuberculosis lung abscess and Boeck s sarcoid involving the lungs These 25 patients accounted for 32 recurrent attacks

The shortest interval between essential recovery from one attack and onset of another was 7 days and the longest 18 years Of the 12 recurrent attacks which occurred within two months of the preceding attack 8 were in subjects with bronchiectasis and in 4 of these

(3) Ann I t Med 16 173 J r

the same type of pneumococci was isolated in each of the attacks Twelve of the 27 recurrences after two to six months were in subjects with chronic pulmonary disease but only 12 of the 153 attacks that occurred after six months were in patients with chronic pulmonary disease Successive attacks were associated with the same pneumococcus type 3½ times as often if they occurred less than six months apart as if they occurred more than six months apart This was equally true for patients with or without chronic pulmonary disease This may imply that persistence of pneumococci either in the carrier state or in foci of infection rather than exogenous reinfection accounts for a large proportion of the early recurrences of pneumonia with the same type of pneumococcus

Sixty four per cent of the first attacks were associated with types I II III V VII and VIII while in the recurrences only 51 per cent were with pneumococci of these types Type III accounted for 14 of the 37 cases with the same type in both attacks Two explanations are suggested (1) type III is the most frequent carrier type (2) one third of the cases of type III pneumonia at autopsy are found to have gross or microscopic abscess formation in the lungs There was no difference in incidence of bacteremia in initial attacks and in non fatal recurrences Five patients had bacteremia in both the first and subsequent attacks only one of them of the same type (II) There were 21 deaths in 191 recurrent attacks a mortality of 11 per cent It is concluded that the recurrent attacks were less severe than the general run of pneumonias at that particular hospital, as judged by mortality incidence of bacteremia and duration of acute illness

There is a suggestion in the recent literature that recurrences of pneumococcic pneumonia may be more frequent in patients treated with sulfonamide drugs in their first attacks than was the case with serum therapy Therefore the authors compared the frequency of recur

rences within two years of an initial attack of pneumonia treated with specific serum sulfonamide drugs both serum and drugs and no specific therapy Results of this comparison revealed that recurrences were not more frequent in patients treated with sulfonamide drugs in the first attack than in those treated with serum or with no specific therapy There was however a greater tendency for second attacks to recur at shorter intervals and for the same type to occur in both attacks in drug treated cases than in the others There is no correlation between the antibody response and the tendency of pneumonia to recur Any given case may or may not have a recurrence with the same type of pneumococcus irrespective of whether he develops antibodies after the first attack Moreover recurrences were noted despite the presence of homologous antibodies at the time of onset of the recurrence

Special Types of Pneumonia

Rheumatic Pneumonia Emanuel Z Epstein and Edward B Greenspan[4] (Mount Sinai Hosp New York City) report observations at autopsy on the lungs in 45 cases of acute rheumatic fever selected regardless of presence or absence of clinical and gross pulmonary changes Such a selection has enabled the authors to reconstruct the chronologic sequence of events in development of the pathologic process from the purely microscopic stage in which no clinical signs could have occurred to the stage at which pulmonary damage is clinically manifest The cases were divided into three groups on the following basis (1) absence of previous history of rheumatic fever no evidence of chronic valvular disease and presence of acute rapidly fatal initial attack (14 cases age 19 months to 25 years) (2) previous history of rheumatic fever evidence of chronic valvular disease and rapidly fatal course in the last admission (21 cases age 3 45) and (3) chronic rheu

(4) Arch Int Med 68 1074 1094 Dec 1941

matic cardiovascular disease with the fatal attack lasting a considerable time (10 cases ages from 12 to 51)

From examination of these cases the authors tabulate the pulmonary changes chronologically The first stage consists of passage of considerable fluid into the alveoli septums and interlobular spaces with marked congestion



Fg 3—Hy l m mb pır t ry b h l l g f h ld 4 wh d d d g fi t tt k f h mt f ft 10 d y h p t l

of alveolar capillaries engorgement and diapedesis of erythrocytes and desquamation of large mononuclear cells into the alveoli This alveolitis is nonfibrinous and nonbacterial and strongly suggests alterations in the capillaries with resultant increased permeability and diapedesis of erythrocytes and transudation of albuminous fluid into the alveoli Hyaline membranes are formed in the respiratory bronchioles and the alveolar

ducts in about 50 per cent of cases As the disease i prolonged this stage is followed by thickening and in filtration of the interlobular septums with mononuclear cells with resultant fibrosis and organization The smaller arteries show occasional thickening Gross exam ination of the lungs at this stage reveals many patchy foci of dark red fleshy noncrepitant, nonaerated areas which have a peculiar India rubber consistency This stage was observed in the 14 cases in which death was due to the initial attack and in which no previous valvu lar disease existed

In all remaining cases evidence of previous cardio vascular disease with resultant pulmonary congestion was found with the familiar effects of more or less long standing stasis In many cases the authors ob served also the evolution of an acute stage similar to that in cases of fatal initial attack In nine cases typical hyaline membranes were seen No Aschoff bodies were found in the lungs

Twenty cases of chronic rheumatic cardiovascular dis ease mitral stenosis, in which the patients died of inter current disease or of chronic heart failure without evi dence of rheumatic fever 23 cases of coronary arterial disease in which the patient died of heart failure and 16 cases of hypertensive heart disease with failure were similarly studied to consider the possibility that the pulmonary lesions seen in acute rheumatic fever were a result of the pulmonary stasis of congestive heart disease In none of the control cases was a picture ob served which approached in similarity that seen in acute fatal rheumatic fever

The mechanism of the formation of the hyaline mem branes in the lungs is dependent on the following factors (and not on any specific infection such as rheumatic fever or influenza as previously believed) (1) material capable of taking the characteristic eosin stain (2) air in the alveolar spaces probably under greater than nor mal tension (3) partial obstruction to passage of the

air by semifluid material in the air passages and (4) dyspnea which may be interpreted as violent inspira tory efforts to force air by this obstruction The alveolitis and the formation of hyaline membranes are a result of damage to the capillaries with resultant alteration in vascular permeability Vascular damage was likewise



Fig 4—S m p d g St k g w d g f t l b l bt m f l g due t d m

present in the main pulmonary artery and its branches and in the hepatic capillaries The vascular change cor responds to the involvement seen in the arterial tree in the various organs of the body in acute rheumatic fever It is concluded that a specific rheumatic lung or rheu matic pneumonia cannot be considered to exist in these a es

Staphylococcus Aureus Pneumonia with Special Reference to Its Occurrence as a Complication of Influenza Staphylococcus aureus pneumonia is characterized by a septic temperature cyanosis fairly extensive pulmonary consolidation thick purulent blood streaked sputum, high mortality and a protracted course in nonfatal cases Empyema or multiple pulmonary abscesses are the most frequent complications Blood culture may be negative but sputum culture yields a heavy growth of Staphylococcus aureus *The largest reported epidemic occurred* during the influenza pandemic of 1918 Influenza A virus was isolated from the lungs in two fatal cases (Stokes and Wolman in 1940 and Scadding in 1937) and pre*sumably in another more recently (Pearson et al in* 1941)

Max Michael Jr [5] presents histories of five patients with Staphylococcus aureus pneumonia observed at *Peter Bent Brigham Hospital* during a brief epidemic of acute respiratory disease during which influenza A virus was isolated from a fatal case elsewhere and from one case of influenza uncomplicated by pulmonary changes at the Hospital At the same time a large number of cases of staphylococcic pneumonia were seen in another clinic in Boston One of the five patients died of overwhelming infection soon after admission, the other four were treated with sulfathiazole and of these one died and three made good recoveries including one patient in whom empyema cleared with aspiration during sulfathiazole therapy To determine whether the staphylococcic pneumonia in these cases was secondary to influenza serums taken at different stages of the disease were studied for the presence of neutralizing antibodies for influenza virus In the three cases in which serum was obtained the results of *neutralization tests* in mice proved that influenza A infection had immediately preceded the pneumonia Sulfathiazole definitely shortened illness in 3 cases in which recovery occurred

(5) J A M A 118 869 874 M 14 19[illegible]

[Clemmons and Weems (*Journal of Pediatrics* 20 281 90 March 1942) have studied staphylococcic pneumonia in infants and draw attention to the incidence of pneumopyothorax in these cases —Ed]

Experimental Aspiration Pneumonia Fluorescence and Pathology were studied by Irving J Wolman and Anna B Bayard[6] (Univ of Pennsylvania) The fluorescence of lipid pneumonia lesions in gross pathologic

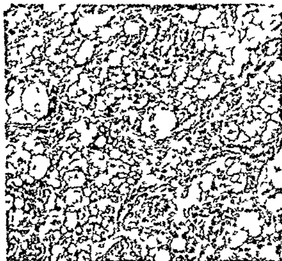
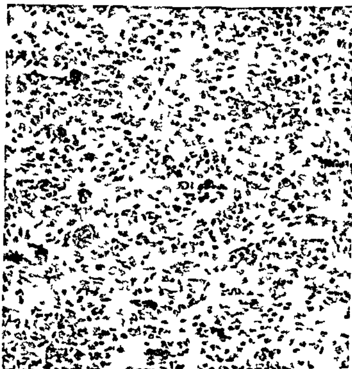


Fig 5—Lung ght m nth fte thre inhalat s f mineral oil at weekl t sl M f cu lated m n cle ll erts ing l g d m l gl bul fill l eo l eol walls thi ke d d fib ed Almost id t l appea e w baerved n l mo tha ep c m n deep y st ning l a e eo n ph l

material was previously described by Wolman and Stevens When affected human lungs are examined under ultraviolet light in a dark room the consolidations stand out as patches of pale yellow gray white or greenish fluorescence That method of examination can show up small spots of involvement which escape detection under ordinary illumination

(6) Am J M Sc 0 54 553 Octobe 1941

The foreign substances used in the authors experi ments on rabbits were cod liver oil, mineral oil canned evaporated milk diluted with equal parts of sterile water fresh unsalted melted butter and centrifugated autoclaved market milk containing less than 0 01 per



F g 6—Lu g tw d ys aft ngle b lat n of apo at d m lk al e l jamm d with te e fl mmat y d te n t ng f ne t ph l e l flu d b ph l gul m d m t ph go yt

cent butter fat these being the substances most fre quently aspirated by children either by way of oily nose drops or by choking or swallowing improperly oily or fat containing material One to five instillations were given spaced one to seven days apart The oils were dropped through each nostril in 1 cc doses milk

preparations in 5 cc quantities The animals were killed at progressive intervals of two days to one year following final treatment by means of intravenous injection of air The lungs were removed immediately afterward and their gross appearance noted in ordinary light and under the fluorescent lamp The lamp employed was a simple dark lamp as used by geologists The ultraviolet ray observations were repeated on frozen and formalinized specimens

The distribution of the foreign materials and of the pneumonic reactions to them proved to be more or less the same with all substances tested All parts of the lobe were involved without noticeable selective localizations in the hilar regions Wide fluctuations in size and distribution of the pneumonic patches were observed with each of the substances some pairs of lungs being flooded with specific consolidations whereas others displayed only isolated spots The fluorescence usually grew more prominent when the tissues had been preserved for several months



F g 7—Lu g tw day ft gle i h l t n f boiled f t f ee w' milk d i l sa t se th w h whol milk, t phil l b d t d b phil déb d ffi ult t d t fy

The cod liver oil pneumonia patches were larger than any of the other aspiration pneumonia patches they looked yellow or yellow brown in both the fresh and formalinized specimens Under ultraviolet light they

fluoresced brightly showing yellow pale yellow cream or yellow brown color Patches produced by mineral oil aspiration appeared gray white and bloodless on gross specimens easily visible against the pink spongy lung parenchyma Under ultraviolet they appeared as gray spots tinted at times with an added green, green blue or blue color Lungs removed from animals in which evaporated milk was instilled showed gray white pneumonic mottling which remained paler than the surrounding tissue after fixation in formalin Under ultraviolet light the pneumonia had a white color The patches obtained by aspiration of butter were dark gray in the 12 month old specimens no lesions could be seen Under ultraviolet a faint gray white color tinged with green was noted in the early lesions while in older specimens the color could hardly be detected The gross and fluorescent appearances of pneumonia produced by autoclaved fat free milk were identical with those of sterile evaporated milk and no fluorescent lesions could be found after 30 days



F g 8—Lu g tw days aft gl nhalat on of m lted butt r wh h st n d ply eo o- ph l c d qu kly l quefied M nonucle lls w thin lacun pock t al g m gins of d ps ell la re ponse con usts alm t ti ely f m no- cyt ud eo ph l

Histologically cod liver oil provoked a violent necrotizing reaction which partially cleared to leave chronic granulomatous deposits which could be detected as late

as one year following the experiment It was the only lipid in this series to possess acid fast staining properties with carbol fuchsin Mineral oil produced little acute inflammation and remained indefinitely as unabsorbable foreign material Evaporated milk stirred up a distinctive transient inflammatory reaction in which the presence of small numbers of phagocytes holding fat could be considered as being entirely a response to its contained butter since no lipophages were in the similar though milder experimental lesions produced with autoclaved fat free milk Butter gave rise to an immediate mononuclear response also of transitory nature With the scarlet red stain butter fat appeared dark red cod liver oil orange red and mineral oil orange yellow demonstrating decreasing solubility in the order named The effects of repeated inhalations were not strikingly dissimilar from those following single inhalations When the pathologic appearances changed quickly with progress of time there were lesions of various ages existing side by side When the tempo of reactive change was slower it was impossible to distinguish between the lesions of single and multiple inhalations

The morphologic changes following milk aspirations whether of normal fat content or fat free were of a character most unlike those of the oils and fats studied There were no lipid deposits and the feature of chronicity was lacking The pulmonary reactions were due to irritation from the contained butter fat and from other components of milk Milk aspiration lesions should not be included under lipid pneumonias The pathologist should make specific diagnoses such as mineral oil pneumonia cod liver oil pneumonia and milk aspiration pneumonia

fluoresced brightly showing yellow pale yellow cream or yellow brown color Patches produced by mineral oil aspiration appeared gray white and bloodless on gross specimens easily visible against the pink spongy lung parenchyma Under ultraviolet they appeared as gray spots tinted at times with an added green green blue or blue color Lungs removed from animals in which evaporated milk was instilled showed gray white pneumonic mottling which remained paler than the surrounding tissue after fixation in formalin Under ultraviolet light the pneumonia had a white color The patches obtained by aspiration of butter were dark gray in the 12 month old specimens no lesions could be seen Under ultraviolet a faint gray white color tinged with green was noted in the early lesions while in older specimens the color could hardly be detected The gross and fluorescent appearances of pneumonia produced by autoclaved fat free milk were identical with those of sterile evaporated milk and no fluorescent lesions could be found after 30 days



F g 8 —Lung tw days fte s ngle i hal t n f m lted b tt wh h sta ns d ply eo o- ph l nd qu kly liquefied Mo n l lls w th n l cun pockets l g m g f d ps c ll la espon ns ts alm t t ly f mono- yt s d eo n ph ls.

Histologically cod liver oil provoked a violent necrotizing reaction which partially cleared to leave chronic granulomatous deposits which could be detected as late

States Warfield T Longcope[8] has observed 40 cases at Johns Hopkins Hospital 3 were fatal and autopsy was performed Age of the patients varied from 17 to 70 most were *young adults* *The incubation period lasts* two to three weeks The acute phase is usually preceded by a few days of malaise Symptoms at onset are a dry *annoying unproductive cough fever headache general* aches and discomfort and occasionally abdominal pain and nausea Chill at onset and pain in the chest are *rare and blood tinged sputum is unusual* In some patients the lungs appear normal in others there may be slight dulness with suppressed breath sounds over one of the lower lobes *There may* be actual leukopenia but mostly the leukocyte count is normal The impression is that of influenza typhoid fever or tuberculosis A roentgenogram of the chest invariably shows a shadow which may be small at the root or periphery of the lung or large and mottled involving a fair portion of the lower lobe The subsequent course may be mild moderately severe or very severe even fatal

In mild cases despite the x ray findings physical examination of the chest may be negative In others explosive rales characteristic of the disease are heard *in the region of the* x ray shadow *during the last few* days of the disease Mostly there is an area of dulness over one of the lower lobes or in the axilla with sup*pressed breath sounds or distant bronchovesicular or* tubular breathing The most distressing feature is the harassing cough with little or no sputum The leukocyte count may *rise somewhat* as the disease *progresses* Sputum and blood cultures are negative The fever begins to fall usually on the third or fourth day defervescence is always by lysis and the temperature is normal on the fifth to tenth day Occasionally there is a subsequent rise Convalescence is rapid and complications are rare

In moderately severe forms the acute stage is pro-

(8) P ct n 148 1 8 J rs 194

VIRAL INFECTIONS

The prevalence of viral infections has stimulated a great deal of experimental and clinical research and several representative articles are presented here —Ed

Pneumonitis in Mice Infected Intranasally with Q Fever is reported by G M Findlay[7] (London) Two strains of rickettsia Q fever were used in the experiments the Australian and the American Similar results were obtained with both Mice were killed 4 10 days after instillation Macroscopic examination of the lungs showed small areas of consolidation distributed irregularly throughout the lobes On microscopic examination the areas showed a somewhat nodular arrangement in association with terminal bronchi and bronchioli The bronchi contained fibrinous deposit cellular exudate and nuclear debris The cells lining the bronchi showed in places considerable desquamation Many of the alveoli were filled with serofibrinous exudate with only few cells in these areas there was only a slight reaction in the interstitial tissue In other areas the alveolar spaces were almost completely obliterated by interstitial reaction The interstitial tissues were crowded with small lymphocytes large mononuclear cells a few plasma cells few polymorphonuclear cell and occasionally there were small nodules composed of dense masses of cells and nuclear debris The cell lining the pleural surface of the lungs were prominent and at some points appeared to have undergone proliferation In sections stained by Giemsa s method rickettsiae were present in large mononuclear cells on the pleural surface of the lung in alveoli and the lumens of the bronchi

Pneumonitis or Virus Pneumonia There is a more or less prevalent form of atypical pneumonia which has occurred in small epidemics throughout the United

(7) Tr Roy Soc Trop Med & Hyg 35 213 18 Jan ry 194

Pearson in atypical cases of bronchopneumonia in California In the present series inoculation of ferrets with solidified lung from one of the fatal cases gave negative results indicating that the disease is not caused by influenza virus Other experiments failed to show the presence of rickettsial infection cytoplasmic inclusion bodies or any other virus

Treatment of this form of pneumonia with sulfonamides is of no avail Because of obvious contagiousness of the disease strict isolation is imperative

Current Investigations of the Influenza Problem C H Stuart Harris[9] reports clinical and pathologic studies on patients with acute respiratory infection admitted to a military hospital during the winter 1940 1941 Most of them admitted during November and December had exudative tonsillitis pharyngitis Vincent s angina or quinsy In January an abrupt change in the clinical type occurred and during January and February the form of the curve and the clinical findings were typical of epidemic influenza The average clinical type was a short febrile illness lasting two to four days with complaints of general malaise headache muscular pain and cough The facies was characteristic with flushing or suffusion of the face slight cyanosis of the lips and glistening suffused conjunctivas There was usually discharge or obstruction in the nose and the fauces were injected but not very sore The invariably present cough was short and dry but rarely paroxysmal or painful and there were usually scattered rhonchi or rales in the chest at the early stage of the disease During March cases of exudative tonsillitis and quinsy which were almost entirely absent during the preceding two months reappeared

Investigations for presence of influenza virus were carried out by Stuart Harris on garglings collected during the various months using the Burnet technic of amniotic inoculation of developing chick embryos In

(9) J R y A my M C rp 77 1 3 134 S pt mber 1941

longed for a week or more Secondary rises in temperature are common The lower lobes are again the most common seat of the lesion but the process may spread from one side to another and from the lower to the upper lobes Outspoken patchy solidification of the lung may be detected by physical examination Temperature elevation persists from 6 to 8 days occasionally for 15 to 18 days The spleen may become palpable and the clinical picture suggests typhoid fever The leukocytes show the same course as in the milder forms Complications may occur Examination of the blood and sputum and the agglutination reactions are negative

In severe infections the disease runs an alarming course with racking exhausting cough rapidly spreading lesions in the lung cyanosis dyspnea or asthmatic breathing and great prostration The acute illness lasts about 2 weeks and fever may persist for 18 to 25 days The leukocyte count is like that in the milder forms Bacteriologic and agglutination reactions are negative Although sputum cultures in the later stages may show pneumococcus or Staphylococcus aureus these are considered secondary invaders Complications like pleurisy thrombosis of the lower extremities, migratory arthritis meningismus and coma are not uncommon

The pathologic lesion in this type of pneumonia is a hemorrhagic bronchopneumonia with red blood cells mononuclears coagulated fluid and considerable edema in the alveoli Polymorphonuclear leukocytes are almost entirely absent from the alveolar exudate but often fill the bronchioles

Various types of virus were described as the possible cause in the aforementioned epidemics The virus of Q fever was reported by Dyer Topping and Bengtson in an institutional outbreak of pneumonitis Cytoplasmic inclusion bodies were described in alveolar epithelium in pneumonitis of infants by Goodpasture Auerbach Swanson and Cotter and by Adams A virus similar to that of psittacosis was recovered by Eaton, Peck and

covered five epidemics in each of which there were 25 to 35 student nurses who had the disease

TREATMENT —The nurses are instructed to report to their superiors on first appearance of symptoms and are immediately put to bed in the institution They are kept in bed until they have a minimum of one full day of normal temperature The following order is entered on the chart rest in bed no company sodium bicarbonate 1 Gm and sodium citrate 2 Gm every two hours when awake acetylsalicylic acid 0 3 Gm when needed for discomfort codeine sulfate 0 03 Gm if there is much pain The alkalis are given in seltzer water or dry ginger ale and the acetylsalicylic acid is given in fruit juice If there is sore throat 5 per cent solution of silver nitrate is applied once daily Should there be sufficient rhinitis to interfere with comfortable breathing a glucose solution of ephedrine is instilled into the nares once or twice daily A laxative or enema is used only if there is constipation or other definite indication Patients are instructed not to blow the nose with violence so as to lessen the tendency to sinusitis or otitis media and to cover the face properly when coughing or sneezing A liquid diet is given when the temperature is under 100 F Water and fruit juices are given freely

Analysis of the 168 cases indicates an average duration of fever of 1 94 days and an average hospitalization of 3 49 days the longest period of hospitalization was 11 days There was no proved pneumonia Two patients showed high temperature (highest 104 6 F mean 100 6 F) pulmonary congestion and other suggestive findings with negative x ray pictures These were given sulfathiazole and the temperature became normal in 12 hours and except for slight secondary elevations remained so

only two garglings derived from January collections were positive results obtained One of these at once produced the characteristic histology of influenza virus A infection of the chick embryo and transmission to other embryos was successful The second gargling produced no lesions in the first and second generation of chick embryo but characteristic lesions were found in the third generation and thereafter transmission was successful It was also possible to adapt these two strains to mice Andrewes in London obtained typical ferret responses with the two chick strains and another gargling from the Stuart Harris series and demonstrated that they were serologically related to the P R 8 laboratory strain of influenza A virus

Thirty four pairs of serums (one sample taken during the acute stage of the disease and the other 6 14 days later) were collected in representative cases during January and February Of these 27 showed fivefold or better rise of antibody to virus A The three patients from whom virus was recovered showed sharp serologic changes to virus A

Treatment of Influenza is discussed by Oscar W Bethea and Ralph Greenlee[1] (New Orleans) There is no satisfactory prophylaxis or specific therapy for the disease the methods being largely empiric The first considerations in prophylaxis are avoidance of exposure and isolation of patients The value of vaccines is still a moot question The authors agree with Cecil that vaccines apparently have a degree of efficiency not only in preventing infection but especially in reducing the incidence of complications such as pneumonia resulting from secondary invasion of bacteria Prophylactic use of serum is especially recommended in the presence of an oncoming epidemic

As regards therapy proper the authors outline their procedure which was used in treating 168 influenza patients all of whom were student nurses The study

(1) New Orleans M & S J 94 17 1 November 1941

of lung tissue while the usual levels of histamine in the adult cats vary from 15 to 35 γ Similar observations made on autopsy material of new born and stillborn infants suggest a possible correlation between the rare occurrence of postoperative pulmonary complications in infants and young children and their increasing frequency with age Other experiments revealed that parenterally administered histamine fails to accumulate in the lung

Comparative preoperative determination of the sub tidal lung volume before and after avertin anesthesia preceded by sedation carried out in adults with negative respiratory histories and chest findings revealed in most subjects a reduction of the pulmonary subtidal volume by approximately 20 per cent due to the imme diate effects of the anesthesia Other effects of avertin administration on the respiratory mechanism were a decrease in oxygen consumption and a decrease in minute respiratory volume An immediate reduction in subtidal lung volume was also found as a result of operation under local procaine anesthesia with pre liminary morphine sedation

The exudative and obstructive phases of postopera tive pulmonary complications are commonly followed by bacterial invasion of the lung In a series of 52 postoperative pulmonary complications in which typ able pneumococci could be recovered from the sputum the wide distribution of the types supported the assump tion that the pneumococci are secondary invaders from the nasopharyngeal flora

[While some are inclined to attribute postoperative pulmonary infections to obstruction of the bronchi the importance of exu dation into the bronchi and alveoli has not been sufficiently em phasized previously Collapse of alveoli alone does not favor infection but stagnation of exudate in them and in the bronchi does —Ed]

Postoperative Infections of the Respiratory Tract in Relation to Inhalation and Spinal Anesthesia A study of 631 cases of abdominal operations at Duke Hospital

POSTOPERATIVE PULMONARY COMPLICATIONS

Studies on Etiology of Postoperative Pulmonary Complications Gustaf F Lindskog (Yale Univ) assumes the existence of some common basic factors responsible for postoperative complications in all types of operations intra and extra abdominal the usually accepted mechanical factors which predispose toward pulmonary hypoventilation become secondary in explaining the preponderantly higher incidence in the intra abdominal group Factors which are inherent in all operative procedures and which conceivably could be etiologic in postoperative pulmonary complications are (1) tissue trauma and absorption of the chemical products of cellular disintegration (2) anesthetic agents local and general (3) pre and postoperative sedation (4) postural restriction

Lung tissue has a high content of histamine or histamine like extractives which may be liberated in perfusates by the action of various toxins such as snake venom staphylococcus toxin and the bronchial insufflation of hydrocarbon and other vapors The action of liberated histamine locally on the lung induces bronchiolar constriction bronchial hypersecretion and pulmonary arterial constriction These effects in a lung already depressed by sedation and various mechanical factors may lead to lobular and lobar obstruction and its sequelae Experiments on the effects of operative manipulations on lung histamine in cats showed no significant changes in the levels of lung histamine due to manipulations However an age factor was found to be responsible for the apparently spontaneous variations in histamine content from animal to animal Assays on the lungs of new born kittens showed that histamine was either absent or was present in amounts of 5 γ per Gm

(2) J Thorac! S rg 10 635 640 August, 1941

gen examination The incidence of postoperative respiratory infections was found to be approximately 2½ times as frequent after spinal anesthesia as after inhalation anesthesia The incidence of postoperative respiratory infections was markedly greater than in the previous series of patients who had no preoperative respiratory infections at time of operation As in the previous series age sex and other factors had no significant effect on the incidence of postoperative respiratory infections The findings suggest that presence of low grade preoperative infections of the respiratory tract of the kind not generally considered contraindications to even elective operations is of sufficient significance as a factor in development of acute postoperative infections of the respiratory tract to warrant further analysis as to the choice of anesthesia

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SUPPURATIVE DISEASE

Pulmonary Abscess and Tuberculosis A A Raimondi and R Scartascini[4] state that cases of pulmonary abscess in which tuberculosis develops should be differentiated from those of tuberculosis in which abscess develops The first group is more frequent The focus of suppuration by progression and extension comes in contact with a tuberculous focus which for a long time had been encapsulated and inactive The bacilli thus liberated produce distinct lesions If dissemination is intracanalicular the foci localize near the abscess if hematogenic generalized or circumscribed miliary lesions are produced The bacilli may be expectorated from the bronchi without colonization occurring All conditions likely to upset the equilibrium e g suppuration involving a considerable part of the lung resulting in profound alteration of the general condition can cause activity in an old tuberculous lesion which had been kept inactive by the defensive powers of the or

(4) R méd [illegible] 7 331 January 194[illegible]

is presented by John Lyford, III[3] Included were only those without infection of the respiratory tract at the time of operation. Postoperative infections of the respiratory tract were considered to have occurred only when the patients showed definite acute infections of the upper respiratory tract or pulmonary signs on physical or roentgen examination as recorded in the postoperative progress notes. Approximately the same proportion of patients without infections of the respiratory tract at the time of operation acquired postoperative infections of the respiratory tract with inhalation as with spinal anesthesia. However, when the relative proportions between the single types of anesthesia are compared it becomes evident that the incidence after spinal anesthesia was 35 per cent greater than that after cyclopropane anesthesia and 23 per cent greater than that after ether anesthesia. The incidence of postoperative infections of the respiratory tract was unaffected by age or sex, length of operative anesthetic time, preoperative complications, kind or amount of spinal anesthetic agent, preanesthetic medication or blood pressure changes during anesthesia.

Pre- and postoperative infections of the respiratory tract in relation to inhalation and spinal anesthesia were investigated in another series of 120 cases in which abdominal operations were performed under ether, cyclopropane or spinal anesthesia on patients who had been shown to have low grade chronic preoperative infections of the respiratory tract. Signs of low grade infections of the respiratory tract looked for in the preoperative records were: (1) exudate and injection of the tonsils, (2) chronic postnasal discharge and (3) pulmonary rales characterized as being associated with chronic bronchitis. Postoperative infections of the respiratory tract were considered to have occurred only when the patients had definite pneumonia, acute bronchitis or acute coryza determined by physical or roent-

(3) A h S re 44 35 43 J u y 1942

in the Southeast It has its origin in the oral cavity and is often nonpathogenic to the host The infection invades both lungs with a diffuse nodular studding

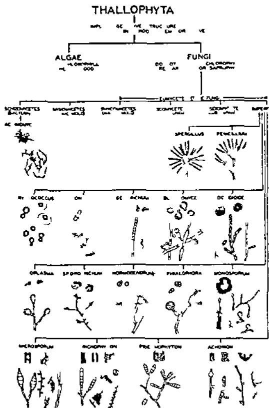


Fig 9—(Courtesy of American Roentgen Ray Society)

throughout If untreated it gradually produces chronic interstitial fibrosis Incidence of blastomycosis infections is second in this region It usually appears in the bronchi through inhalation of the spores but often enters through the skin or alimentary tract The infection may

ganism Cases of tuberculosis in which abscess develops are uncommon Tuberculous tissue is refractory to pyogenic or putrefactive flora from a complicating abscess Treatment should take in account the concurrence of pulmonary abscess and tuberculosis In view of the relative frequency of tuberculous complications in cases of pulmonary abscess the authors advise early treatment with the objective of preventing this complication. On the other hand in the rare cases in which abscess complicates tuberculosis active surgical treatment is contraindicated even simple drainage is not without danger In cases in which the abscess is in healthy pulmonary tissue the decision whether treatment should be surgical or not depends on the behavior of the tuberculous lesion

[A study by Baum and Amberson (*American Review of Tuberculosis* 40 243 2 9 March 194_) bears out the correctness of the conception that necrotic suppurative processes in the lung may erode tuberculous foci cau ing dissemination This is an important consideration in the treatment of pulmonary abscess when tubercles are known to exist nearby —Ed]

FUNGOUS INFECTION OF THE LUNGS

Diagnosis and Treatment of Pulmonary Fungous Infections are outlined by Robert J Reeves[5] (Duke Univ) These conditions closely simulate sarcoidosis and often cannot be differentiated from tuberculosis or from primary or metastatic malignancy Infection usually occurs through aspiration or inhalation of spores which sets up primary foci in the lungs Dissemination may then occur through the blood and lymph channels and may involve any organ in the body Gastric washings are frequently necessary to obtain material for study Cavitation occurs frequently in the lungs and with the surrounding infiltration is indistinguishable from tuberculosis

Monilia infection is the commonest of these infections

(5) J Ten ee M A 35 2?7 209 J e 194

administered Blastomyces vaccine is made up by preparing the filtrate and killing the organisms The combination of iodides and x ray therapy is effective for the local lesions in blastomycosis and actinomycosis however the systemic disease may persist

Pulmonary Cavitation Associated with Coccidioidal Infection William A Winn[6] (Springville Calif) reports observations made in 13 cases Coccidioidal cavitation as compared with the lethal cavitation of tuberculosis is relatively benign Unlike the latter condition which usually occurs during reinfection or in the adult type of the disease most coccidioidal cavitation develops during or shortly after the primary stage of pulmonary infection Prognosis is favorable and treatment should be conservative except in the presence of persistent pulmonary hemorrhage or the occasional large cavity when pneumothorax is advisable It is not necessary to isolate the patient or to separate him long from his usual mode of living and employment Infection is produced by the chlamydospores of the fungus (reproductive cycle) and acute infection does not pass from person to person via sputum containing the endospores or spherules (parasitic phase) The fungus occurs naturally in the soil where the disease is endemic and the chlamydospores are easily transported by wind and dust and inhaled Occasionally infection may occur through skin cuts or abrasions It is important to remember the possibility of coccidioidomycosis whenever pulmonary cavitation occurs and tubercle bacilli have not been demonstrated especially in endemic regions such as the San Joaquin Valley parts of Arizona and Texas and the Chaco regions of Argentina Coccidioidal granuloma is relatively uncommon and must not be confused with primary coccidioidomycosis pulmonary cavitation in association with granuloma is unusual

Primary infection by Coccidioides immitis is commonly accompanied by symptoms of the respiratory tract

(6) A h I t M d 68 11 9 1 14 Dec mbe 1941

manifest itself by an insidious chronic condition or may be acute with rapid onset Clinical symptoms may simulate any acute disease while the chronic type produces malaise cough pain in the chest and irregular fever X ray studies of the lung may show diffuse nodular infiltration or consolidation The organism may be found in the sputum or may be obtained by bronchoscopic examination Skin tests and blood agglutinations should be positive When smears and biopsy are negative cultures are made on blood agar The serum should contain complement fixing antibodies for strains of blastomyces

Actinomyces is frequently found around the jaws In three patients Reeves found them primary in the appendix The pulmonary lesions are usually dense consolidating masses arising in the perihilar lymph nodes and invading the lungs and frequently breaking down leaving large cavities Examination of the smear of the sputum shows the sulfur granules Culture shows clumps of granules with many mycelia Aspergillus infection is frequently found in the great wheat belt The lesions in the lungs when healed leave small calcified areas Coccidioidal granuloma is endemic in certain parts of the United States chiefly California but is found also in the Middle West It too is acquired through inhalation of the spores and when primary in the lungs often runs a rapid course treatment is ineffective The other less common fungi sporothrix torula geotricum and histoplasma may be detected only by thorough search and studies by a trained mycologist

Treatment of all mycoses consists of administration of iodides and other agents With monilia and blastomyces infections desensitization must be done first Monilia vaccine is obtained by washing the Sabouraud slant culture in normal saline and killing the organisms in the filtrate The solution is used for the skin test and if a sharp reaction is obtained, desensitization is carried out with smaller doses Potassium iodide is then

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(6) [illegible]

usually bronchitis with a slightly productive cough There may be systemic reaction Roentgenograms of the lungs may show only changes in the area of the lung root such as peribronchial haziness or definite patches of pneumonitis often in nodular form Occasionally, exudative lesions involving lobules or even entire lobes associated with early cavitation are present Recovery is followed by walling off or clearing of the primary focus or localized caseous or calcified foci or cavitation

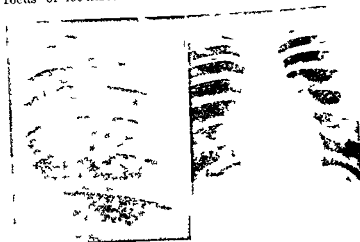


Fig 10 (left) —Film on Ap 2 1940
Fig 11 (right) —Same case Aug 24 1940

may remain as roentgenographic evidence of the primary infection Cutaneous sensitivity to coccidioidin develops in 7 to 14 days after onset Erythema nodosum or multiforme occurs in 2 to 5 per cent of cases usually appearing 5 14 days after onset and lasting 1-4 weeks That primary infection may be asymptomatic is attested by the high percentage of reactors in San Joaquin Valley

There may be a few or no symptoms associated with residual coccidioidal pulmonary cavitation after the acute primary infection has subsided In one case in

which cavitation occurred in conjunction with the acute primary infection the clinical picture differed little from the one described In most cases the patients gave a definite history of hemoptysis varying from frequent streaking to frank hemorrhage in about half the cases there was a history of one or more respiratory infections occasionally resulting in a prolonged period of cough and expectoration All patients with latent cavitation (10 cases) appeared in good health They had no systemic symptoms and were able to follow ordinary occupations except when forced to stop work because of recurrent pulmonary hemorrhage (5 of the 10 cases) Criteria for diagnosis of latent cavitation were based on the roentgenographic appearance of a thin walled cystlike cavity which appeared punched out or dead with little or no surrounding collateral reaction Such cavities are to be considered as more or less benign stabilized structures the end results of a small focus of destruction produced by the primary coccidioidal infection They may disappear spontaneously if bronchial occlusion becomes total and permanent Primary infection may also become a deep seated localized infection of the bronchial wall eventually producing a small area of bronchiectatic change associated with destruction and sacculation of the bronchial wall

The clinical histories of the 13 patients are presented Cutaneous sensitivity to coccidioidin was demonstrated in all cases Bacteriologic studies of sputum or gastric contents disclosed the presence of the fungus Serologic studies of the blood were usually confirmatory In no case did clinical observation or roentgen follow up varying from few months to several years disclose evidence of dissemination of infection or progression of the disease

[Aside from the hazard of hemorrhage cavitary residuals of this infection might in time become the seat of secondary infection particularly following acute respiratory diseases —Ed]

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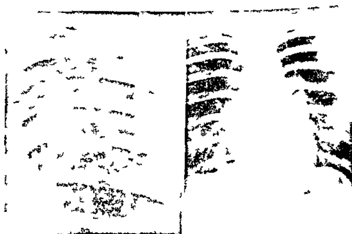


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Pneumoconiosis[7] On reviewing the pertinent literature the Committee on Pneumoconiosis found that most investigators agree that all dusts are harmful but that only silica and asbestos dusts cause a disabling pulmonary fibrosis that can be diagnosed as a disease entity Others claim that other dusts (coal dust for instance) also cause fibrosis A few investigators (notably the French) believe that tuberculosis must be present in the lungs before silicosis results from breathing dust The theory of mechanical action of dust still persists although that of chemical action of silica dust through its solution in body fluids has almost superseded the mechanical theory Some believe that the injurious effect is a combination of mechanical and chemical action The term lung fibrosis has been suggested instead of pneumoconiosis to avoid confusion resulting from the use by some of silicosis for all dust diseases and pneumoconiosis for disease due to inhalation of silica dust

As a result of experiments on the reaction of peritoneal tissue to injected dust the Public Health Service divides dusts into absorptive proliferative and inert Correlation of these experiments with the results of x ray or postmortem examination of workers exposed by inhalation to high concentrations of the same dusts for protracted periods reveals that no cases of pneumoconiosis have been reported among workers exposed solely to dusts of the absorptive group All of the dusts of the proliferative group are known to produce a nodular pulmonary fibrosis certain dusts of the inert group are known to cause a diffuse interstitial pulmonary fibrosis or a mixed nodular and diffuse fibrosis such as is produced by anthra[illegible] coal containing free silica Interpretation of [illegible] response pro

(7) Am Pub Health A [illegible] Book 1941 [illegible] 1 4

duced by a dust in the peritoneal tissue in animals can be used as an index to determine the potential harmfulness of an industrial dust to which workers are exposed An absorptive reaction indicates that the dust is relatively harmless a proliferative reaction that it is definitely harmful and an inert reaction that it is less hazardous than those producing a proliferative reaction and more dangerous than those of the absorptive group

Certain dusts as coal dust once believed to be harmless or even to have an antidotal effect when inhaled with silica dust have been found to be nonprotective or even harmful Aluminum dust however is an apparent exception and experiments with its use in the treatment of simple silicosis are encouraging However since it cannot be applied to silicotics who have tuberculosis as its effect on tuberculosis is unknown most of the silicotics are ruled out as possible candidates for this treatment

In Canada efforts are being made to control tuberculosis in the community as well as among the miners as this disease rather than silicosis is considered the major problem It is tuberculosis that disables the silicotic

Studies by the Public Health Service and other investigators in the dusty industries reveal that dust concentration and length of exposure are in general the most important factors in the etiology of silicosis as well as in its prevention

[A good deal of inte e t has been centered recently on pulmonary damage caused by inhalation of certa n talc dusts S hul and Williams (*Journal of Industr al Hyg ene a d Toxicology* 4 ,5 79 April 194) find that talcs containing the least amounts of carbonate cause the greatest amount of fibros s —Ed]

Significance of Chemical Examination in Diagnosis of Silicosis Leroy U Gardner and Andrew J Redlin (Saranac Lake N Y) analyzed 150 lungs 58 of which revealed no evidence of chronic disease no excess of dust visible on microscopic examination and were taken from

(8) J I d t Hyg & T 1 4 1 5 130 J 1942

persons with no known exposure and 92 of which were from persons employed for five or more years in dusty industries with an appreciable free silica hazard demonstrated by production of silicosis The data obtained in this series indicate that the amount of total silica in the tissues does not parallel the extent or severity of tissue reaction in the individual case While in general the silicotic lung tends to contain more total silica than the nonsilicotic one there is no particular quantity above which most of the positive cases occur The often quoted figure of 1 per cent of dry lung tissue is of no diagnostic significance Attempts to correlate exposure factors with the values for ash and total silica in the lungs are rarely successful Admixture of inert silicates with the inhaled quartz and probable variations in effectiveness of individual upper respiratory protection tend to defeat this purpose The only logical basis of comparison is the free silica content of the silicotic tissue Analysis by chemical methods and x ray diffraction now permits quantitative differentiation between the free and the combined silica in the same mixture

The percentages of both forms of silica were determined in 30 silicotic lungs in most of them quartz constituted one half to one fourth of the total silica In persons who had been engaged in working rocks high in silicates the combined silica was in greater excess Not enough cases have yet been analyzed to learn whether satisfactory correlation with tissue reaction will be possible but the evidence suggests that it may not Use of dry lung tissue as the basis of reference is unsatisfactory, because pathologic reaction in this organ alters both its structure and its specific gravity Animal experiments have shown that during prolonged exposure to quartz the quantity of silica in the lungs increases until fibrosis has developed after this occurs the percentage of silica in the dry lungs steadily decreases As a consequence the authors believe that present methods of expressing results do not reflect the true dif

ferences in quantities of silica in massive fibrous areas and in more normal lung tissue One other factor is the action of inhibitor substances Experimentally it has been shown that mechanical or chemical coating of the surface of quartz particles will completely neutralize their stimulating properties so that no fibrosis develops

Unsupported demonstration of silica in lung tissue is without diagnostic significance Since both disability and increased susceptibility to tuberculosis are the re sult of alterations in anatomic structure diagnosis of silicosis must remain on a morphologic basis Chemical analysis may be a useful adjunct in disclosing the cause of the fibrosis in complicated cases in which silica ex posure has not been suspected but it can never supplant the ordinary methods of pathologic diagnosis

Silicosis of Systemic Distribution is reported by Ken neth M Lynch[9] (Med College State of South Caro lina)

Negro 30 for six years worked in a sand drying plant where protective measures were not available and where he was subjected to inhalation of fine and blown by hot air At the onset of illness he was treated for fever and malai e thought to be malaria Later cough and rales all over the chest developed and x ray examination of the lungs was thought to show tuberculosis Two months before death which occurred a year after on et of his illness there were signs of complete collapse of the left lung with friction rubs and rales over the entire right lung

Postmortem anatomic diagnosis was pulmonary silicosis acute pleurisy right pneumothorax hypertrophy and dilata tion of the right heart Microscopic examination of the liver showed foreign dustlike material accumulated particularly in the Kupffer cells of the central lobular zone which led to degeneration and necrosis of tissue with hyalinization and early fibrous tissue proliferation The spleen revealed deposits of fine opaque granular dust in the endothelial cells of the sinu es and in nodular bandlike collections stimulating con nective tissue proliferation hyalinization and necrosis in malpighian bodies and the peripheral zone of the trabeculae In the kidneys the same fine opaque material was scattered in the endothelial cells of the glomerular capillaries The

(9) Am J P th 18 313 3 1 M b 194

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Pulmonary Pneumatocele (Bullous Emphysema)

George Lister[1] (Temple Univ.) reports a case

Boy aged 6 months was hospitalized with fever, vomiting and restlessness. According to a report from another hospital he had had pneumonia and empyema on the left side at 2 months. At that time a few days following thoracentesis a roentgenogram showed an air collection behind the heart. This was interpreted as pneumothorax which was subsequently tapped on several occasions and allegedly was smaller on the infant's recent discharge from the hospital. On present admission the findings were temperature 103 F, respiration 72, irritating cough, tympanitic chest, distant breath sounds over the left lower lobe, hyperresonance and exaggeration of breath sounds over the right lower lobe, impairment to percussion and tubular and distant breath sounds over the right interscapular region, fine and medium moist rales throughout the chest, shifting of the heart to the right and distention of the abdomen. The diagnosis was atypical pneumonia with pneumothorax or congenital cyst. The infant was treated with sulfapyridine and antipneumococcus serum type XIV and later with sulfathiazole. He was discharged in good condition six weeks after admission. The roentgenogram on discharge showed the air collection to be unchanged and the last manometric reading of the pressure in the cyst was plus 2 mm. on inspiration and plus 10 mm. on expiration. No air was removed. An attempt to delineate the cyst by producing an artificial pneumothorax one month later was more or less a failure. The infant continued to improve and the wheezing in the chest cleared. The collection of air diminished progressively and six months after discharge both pulmonary fields were clear on physical and roentgen examination.

Lister concludes that according to Pierce and Dirkse's classification of cystic disease of the lung the present case fits into the fourth type. The probable cause of this type was stated to be necrosis of the bronchiolar wall following lobar pneumonia with production of rupture by cough. Lister believes that when an air cyst is diagnosed roentgenographically steps should be taken

(1) Am. J. Dis. Child. 6: 613-616, September, 1941.

lymphoid tissue of the nodes adjacent to the large bronchi was largely replaced by masses of hyaline nodules of various sizes containing fine deposits of particulate matter In none of the organs was there evidence of tuberculosis and no acid



Fig 1 —D po t f art ul t m t r l with ellula d gene tio la lt e n s l s × 744

fast bacilli could be found in sections of the liver and spleen Iron particles were not demonstrable in any of the tissues Microchemical methods of analysis devised by F B Culp disclosed that the silica content of the tissues was significantly higher in the lung liver spleen and even the kidney than in normal controls

attack of profu e bloody diarrhea lasting 10 days Pre ent examination of the stools revealed Endamoeba histolytica cysts The patient was placed on anayodin (oxyquinon sul fonic acid plus 30 per cent iodine and sodium bicarbonate) for two weeks she improved slightly but the abdominal pain persisted A subsequent course of 1 cc emetine hydrochloride intramuscularly for seven days brought dramatic results all chest and abdominal signs and symptoms disappeared the sedimentation rate, hemoglobin content and percentage of eosinophils became normal and stools were negative for ameba

A review of literature revealed that most cases of Loeffler s syndrome may be considered allergic in origin the allergens being as variable as those giving rise to other allergic manifestations As the patient had never previously had asthma or other allergic manifestations the presence of ameba and the results of antiamebic treatment suggest that Endamoeba histolytica was the specific allergen causing her symptoms A thorough in vestigation of each case of transient pulmonary infiltra tion for the etiologic factor is urged

[This is a very unusual case It is well known that the lung does not often become involved in amebic infection except by rup ture of an amebic abscess of the liver through the diaphragm and pleura.—Ed]

Mediastinal and Pulmonary Changes in Erythema Nodosum L W Paul and E A Pohle[3] (Univ of Wis consin) reviewed the literature and found that the present consensus is that there is no one specific infec tion or toxic agent responsible for erythema nodosum in adults In children especially in the Scandinavian countries most of the cases are believed to be due to tuberculosis

In a group of 20 patients (19 adults) admitted with the diagnosis of erythema nodosum for whom chest roentgenograms were made as a part of the diagnostic study 12 showed varying degrees of a mediastinal or pulmonary pathologic condition In three cases these changes were minor and probably not significant In

(3) R d l gy 37 131 137 A gu t 1941

to establish a diagnosis by means of an artificial pneumothorax which will differentiate a tension loculated pneumothorax from a bullous emphysema Once the diagnosis of bullous emphysema is established no active therapy should be instituted unless there is a respiratory or cardiac embarrassment from a mediastinal shift otherwise aspiration may complicate the picture by introducing infection and producing empyema In the present case no aspiration was performed for the last seven months of the disease and recovery was spontaneous and complete

[It is not usually necessary to induce artificial pneumothorax to distinguish bullous emphysema from partial pneumothorax The roentgen picture and the clinical behavior of the case usually suffice to make the differentiation —Ed]

Transient Pulmonary Infiltration A Case with Eosinophilia (Loeffler s Syndrome) Associated with Amebiasis is reported by Amanda Hoff and H Mason Hicks (Bellevue Hosp)

Woman 40 complained of violent paroxysmal cough and low grade temperature of three months' duration The cough was nonproductive and gradually increased in severity frequently ending in vomiting She had a distinctly metallic taste History was negative except for an attack of pyelitis eight years previously The first examination was essentially negative One week later she was found to have a few sibilant rales and asthmatic breathing Sedimentation rate was 28 mm in one hour hemoglobin content 65 per cent and white blood cell count 12 250 with 19 5 per cent eosinophils Chest plates showed a triangular shadow extending outward from the right hilus past the middle of the lung field There were clouding of the right base laterally and anteriorly and a diffuse density in the left second intercostal space The condition remained unchanged during the next two weeks and the patient complained of a dull ache over the region of the liver The eosinophilia rose to 41 per cent Chest plates taken 17 days after examination revealed that the triangular shadow had almost completely disappeared but there was a shadow at the right base medially and anteriorly and diffuse mottling at the left base A more detailed history disclosed that the so-called attack of pyelitis was in reality an

( ) Am R T berc 45 184 192 February 194

attack of profuse bloody diarrhea lasting 10 days Present examination of the stools revealed Endamoeba histolytica cysts The patient was placed on anayodin (oxyquinon sulfonic acid plus 30 per cent iodine and sodium bicarbonate) for two weeks, she improved slightly but the abdominal pain persisted A subsequent course of 1 cc emetine hydrochloride intramuscularly for seven days brought dramatic results all chest and abdominal signs and symptoms disappeared the sedimentation rate hemoglobin content and percentage of eosinophils became normal and stools were negative for ameba

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(3) Radiology 37 131 13 August 1941

three others slight but definite degrees of hilus lymphadenopathy were demonstrated. In six cases moderate to pronounced hilus enlargement was present; in two of these hyperplastic tuberculosis was the etiologic factor of the lymphadenopathy and in four others tuberculosis was believed to be the cause of the erythema nodosum and hilus lymphadenopathy. Figures 13 and 14 show the roentgen picture in one of the two cases in which a tentative clinical diagnosis of lymphoblastoma was made and roentgen therapy given which produced



Fig 13 (left) —F[illegible] n [illegible] dm [illegible] n Feb 5 1935
F[illegible] 14 ([illegible]ght) —S[illegible] m [illegible] June 18 1935 Con[illegible] ble [illegible] med[illegible] l m[illegible]se

considerable improvement. These cases again demonstrate the difficulty of distinguishing between inflammatory and neoplastic mediastinal masses.

In a given case of mediastinal and hilus enlargement the presence of a coexisting or recent erythema nodosum should be of great value in establishing the nature of the adenopathy since even in adults such a combination is most likely to be of tuberculous etiology. Conversely, when roentgen examination of the chest in a patient with erythema nodosum demonstrates hilus adenopathy the tuberculous etiology of the former can be surmised (exclusive of those cases occurring in areas where coccidioidomycosis is known to be prevalent). It

is suggested that all patients with erythema nodosum have roentgen examination of the chest and that follow up studies be carried out even when x rays are negative The cause of erythema nodosum may vary in different countries and in different parts of the same countries The authors conclude that not every adult with erythema nodosum need have a streptococcic or rheumatic background for the skin lesions and that a knowledge on the part of the roentgenologist that a given patient showing an unusual mediastinal mass has an associated erythema nodosum may make an otherwise difficult diagnostic problem easier

[Tuberculosis as a cause of mediastinal and hilar lymphatic swelling in adults is more common than usually conceded Tuberculosis as the cause should be one of the primary considerations — Ed]

Sarcoidosis or Besnier Boeck Schaumann Disease Warfield T Longcope[4] (Johns Hopkins Univ) reports his observations on 31 cases of sarcoidosis 8 of which were reported previously Five patients in the entire series have died to date The clinical diagnosis was confirmed in every instance by histologic examination of a lymph node a nodule in the skin or the organs at autopsy The disease was more common in Negroes than in white persons Ages varied from 10 to 51 Constitutional symptoms such as fever loss of weight anemia and leukocytosis were uncommon even in presence of extensive organic involvement The only blood count abnormality was eosinophilia which in 11 cases formed 6 35 per cent of the cells

Involvement of any or all of the structures of the eye was present in 16 patients being in 12 the first manifestation of the disease Retrobulbar neuritis resulted in blindness in one in five enucleation had to be performed in seven the eye symptoms formed a part of the syndrome known as uveoparotid fever

The mediastinal and bronchial lymph nodes and the lungs were involved to a greater or lesser extent in 28

(4) J A M A 117 13 1 13 7 Oct 18 1941

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F g 14) ht) —Same se, J 18 193 Co de bl dec ease med t l masse

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the duration of asthma was less than one year in 30 per cent of those in whom it was one to five years and in only 22 per cent of those in whom it was longer than five years

In 60 children the bronchi contained mucopurulent or thick mucoid material which often tended to adhere to the bronchial wall Thick viscid intraluminal secretion was present in every child examined bronchoscopically in the midst of an acute attack In every instance the respiratory distress was unmistakably diminished after aspiration of the secretion in some cases it subsided completely The bronchial exudate presented no characteristic bacteriologic picture fungi or tubercle bacilli were not found Despite the presence of thick endobronchial exudate complete occlusion of a bronchus with consequent lobar or segmental atelectasis was not demonstrated roentgenographically in any case Of 20 children in whom bronchography was done 5 were found to have bronchiectasis

This study lends no support to the theory of bronchospasm or broncho edema being the basic asthmogenic factors Probably the presence of mucoid secretion in the trachea and bronchi is intimately related to the creation of respiratory dysfunction The precipitation of an asthmatic attack probably entails some additional mechanical element

Use of Theophylline Ethylenediamine (Aminophylline) in Asthma is reported on by Herman Bernhardt[6] (Veterans Admin Montgomery Ala) Over a period of nine months up to July 1940 aminophylline was used effectively in the treatment of seven consecutively admitted patients with asthma in Veterans Administration Facility Tuscaloosa Ala Five of these cases are reported Two of the patients had asthmatic bronchitis with severe respiratory embarrassment presenting status asthmaticus one asthmatic bronchitis with moderate respiratory embarrassment one asthmatic

(6) M B ll Vet Adm 18 153 155 O tob 1941

BRONCHIAL ASTHMA

Bronchoscopic Aspects of Asthma in Children Emily L Van Loon and Sidney Diamond (Temple Univ) analyzed 100 representative cases The allergic nature of the condition was indicated by definite cutaneous sensitivity to specific allergens In each case bronchoscopy was performed without anesthesia at least two times The youngest patient at the time of initial bronchoscopy was aged 1 the oldest aged 13 Age at onset of asthmatic symptoms varied from 3 months to 1? years and duration of symptoms at first endoscopic examination ranged from 1 month to 10 years Most observations were made between acute attacks direct inspection of the tracheobronchial tree during the actual paroxysm being confined to children whose respiratory discomfort was not relieved by ordinary pharmaceutic means

A persistent cough was present in 27 children Of 40 whose sinuses were examined roentgenographically paranasal sinusitis was demonstrated in 35 Nonspecific inflammatory changes were observed in the bronchoscopic picture in all but nine children There was however no mucosal edema no bronchospasm and no organic bronchostenosis In 36 per cent of the children there was some accentuation of the physiologic posteroanterior narrowing that occurs in the trachea and the larger bronchi during expiration and cough This accentuation varied considerably in degree in different children and was far from constant in each child Even with the tussive narrowing pronounced the tracheal and bronchial lumens always resumed their normal contours and diameters on inspiration The exaggerated expiratory narrowing of the airway appeared to be directly proportional to the brevity of the asthmatic history it was observed in 60 per cent of those in whom

considerably retards the oxidation of adrenalin both in solution and in suspension It is a powerful reducing agent and is nontoxic Favorable results have been de scribed from its independent use in asthma Suspensions of adrenalin base with ascorbic acid in excess deterior ated slowly and were nonirritant to the tissues in con centrations under 15 mg per cc acid Suspensions containing a small quantity of wax added to wool fat render the absorption much slower as if it had some protective effect on adrenalin Peanut oil though ab sorbed as rapidly as most vegetable oils is not readily removed from tissues For this reason it was thought *advisable to make the bulk of the injection as small as* possible The average dose contains a little over 0 2 cc oil The formula is

Adrenalin base	0 010 Gm
Ascorbic acid	0 015 Gm
White wax	0 020 Gm
Wool fat (anhydr)	0 040 Gm
Peanut oil	1 cc

The white wax and wool fat with some of the peanut oil are sterilized at 150 C for an hour the rest of the oil being sterilized separately The adrenalin and as corbic acid are ground to a fine powder in a sterilized mortar and then triturated with some of the cooled pea nut oil The mixture of wool fat wax and oil is added to form a homogeneous suspension The suspension is kept in dark amber vaccine bottles provided with glass beads to allow for shaking If properly prepared the suspension can be injected through a 6/10 bore needle a feature of special value when it is to be given by the patient himself In the hospital the injection is made deep into the gluteus medius The average dose is 0 3 cc comparable to 0 5 cc liquid adrenalin chloride The effect lasts for six to eight hours The initial dose should be 0 1 cc except in status asthmaticus in which adrena lin is tolerated well The effects of an excess of adrena lin in the circulation may be due to overdose contami

bronchitis with mild respiratory embarrassment and one cardiac asthma Based on the results obtained in these cases Bernhardt makes the following conclusions (1) Aminophylline administered intravenously in doses of 0 24 Gm in 10 cc saline solution produces an effective and prolonged response in severe asthmatic bronchitis and status asthmaticus (2) Adrenalin fast asthmatic patients given aminophylline are resensitized to adrenalin (3) In moderately severe asthma aminophylline given intravenously produces as prompt a response as adrenalin while the effectiveness of aminophylline is much more prolonged (4) In mild asthma not adrenalin fast aminophylline given intravenously is not as efficacious as adrenalin (5) In cardiac asthma aminophylline administered intravenously is an effective agent (6) Aminophylline given intravenously in doses of 0 24 Gm in 10 cc saline solution at a rate of 2 cc per minute produces no unfavorable reaction (7) Aminophylline produces no effect on asthma when given orally (8) One aspect of aminophylline therapy in asthma that needs clarification is its modus operandi in relieving asthmatic attacks and restoring sensitivity to adrenalin

Adrenalin Ascorbate Suspensions in Bronchial Asthma Alexander Kennedy[7] (London) points out that although no therapeutic agent has been found which could replace injections of adrenalin in acute bronchial asthma absorption and destruction of this drug are so rapid that its effects are brief and difficult to control The objective of the present study was to find a method of administering adrenalin which would render its liberation into the circulation as slow and its rate of absorption as even as possible during the period of its action The preparation finally arrived at consists of a concentrated suspension of dry adrenalin base with ascorbic acid in peanut oil anhydrous wool fat and a small quantity of white wax Ascorbic acid

(7) Lancet 2 ?79 81 Sept 6 1941

as idiopathic because no etiologic agent can be discovered John S LaDue[3] (Univ of Minnesota) reports a case

Negro 20 was admitted in an unconscious dyspneic and cyanotic state He soon regained his senses and stated that he had always been well until a few months previously when increasing weakness fatigue and headache had developed this was associated with a chronic cough and occasional expectoration of blood tinged sputum For six months before admission he had been employed at a shoe lining parlor using a liquid dye with an acrid and unpleasant odor and



Fig 16 (left)—Film n Aug 18 1937 interpreted normal
Fig 1 (right)—Film Sept 14 1937 show firm soft, nodular filtrat of both lung field

fumes which often made him cough He was convinced that the dye was responsible for his illness which he dated from the time he started to work at shoe dyeing

On admission a small amount of blood tinged sputum was noted in the posterior part of the pharynx The respirations were rapid irregular and shallow The lungs were resonant throughout and numerous medium crepitant rales were heard over both lung fields The hemoglobin concentration was 38 5 per cent and the red cell count 1 990 000 No acid fast bacilli were found in the sputum A roentgenogram of the chest showed a soft nodular infiltration of both lung fields uniformly distributed which was interpreted as miliary tuberculosis Placed in an oxygen tent the patient improved considerably However on the fourth day after admission he

(3 A h I t Med 68 663 673 October 1941

nation of the suspension with water or injection into a vascular area They consist of pallor severe palpitations with precordial distress air hunger and faintness The danger is not great and the patient should be kept as still as possible

The type of patient for whom adrenalin ascorbic suspensions have proved most useful is the chronic asthmatic with some emphysema, whose attacks are predominantly nocturnal A short course of nightly injections often restores normal routine by allowing of unbroken sleep In asthmatics with chronic bronchitis and an annual winter period of invalidism this period can be considerably shortened and the bronchitis cleared by using this form of adrenalin By reducing edema by the hypertonic sucrose method of Keeney and then keeping the patient free from further attacks by injections of adrenalin ascorbate suspension it has been possible to obtain relief in severe cases of status asthmaticus

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DISEASES OF THE BRONCHI—DIAGNOSIS

Bronchiolitis Fibrosa Obliterans The symptom complex of bronchiolitis fibrosa obliterans although well defined is one which usually escapes clinical recognition The disease results from organization of fibrinous exudate in the bronchioles in response to local injury According to the literature on the basis of the etiology cases of bronchiolitis fibrosa obliterans fall roughly into three categories (1) those in which the disease apparently follows inhalation of irritant and damaging substances (such as fumes of nitric or sulfuric acid poison gases or vapor of certain solvents) or ingestion of foreign bodies, (2) those in which the condition complicates certain acute infectious diseases like measles influenza or scarlet fever or occurs in the course of chronic bronchitis or asthma (3) those in which the history is inadequate and those which must be accepted

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F g 17 (ght) —F lm 6 pt 14 1937 sh w f rm soft d l filt at f both l g fi ld

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(8) A h I t Med 68 663 673 Oct b 1941

complained of nausea vomiting and epigastric pain, and on the eighth day the severe respiratory distress returned He died on the ninth day

Autopsy showed both lungs voluminous, exhibiting uniformly diminished crepitation The pleural surfaces and cut sections were coarsely granular because of innumerable uniformly distributed tiny, translucent white nodules measuring 1 2 mm and surrounded by areas of injection Micro-



Fig 18 —Diseased bronchiole early stage partial destruction of bronchial epithelium obliteration of lumen by fibrin and partial organization of exudate

scopically the miliary nodules were formed by lesions of the small bronchioles In the early stages the lumen was filled with fibrin red blood cells and macrophages or the epithelium was partly or totally destroyed and the lumen was filled with epithelial debris fibrin and partial organization of the exudate In later stages the bronchiole was completely obliterated by dense connective tissue and was recognizable only by the peripheral strips of smooth muscle Strips of connective tissue extended from the involved areas into the adjacent parenchyma There was evidence of extensive hemorrhagic pneumonia in most of the sections, and areas of atelectasis and

emphysema were noted about some of the bronchiole The kidneys showed acute hemorrhagic glomerulonephritis

In retrospect it is believed that the disease was due to inhalation of the fumes from the dye dissolved in a volatile solvent (impure trichlorethylene) It is important to include bronchiolitis fibrosa obliterans among the possible diagnoses when confronted with a violent



Fig 19—D se sed b h l l t st g lm t mpl t d struct d epl m t by d n t t p ed b m ll p ll

respiratory distress of pulmonary origin The differential diagnosis based on the chest roentgenogram includes interstitial pneumonia and miliary carcinomatosis In interstitial pneumonia there is usually no such intense dyspnea and cyanosis as in bronchiolitis obliterans in miliary carcinomatosis the primary tumor may often be found and the patients are severely emaciated in contrast to the well nourished appearance of the patient with bronchiolitis fibrosa obliterans

[This case would be described by some at least on the clinical evidence as an example of Ayerza s syndrome ("black cardiac)

but it is now generally understood that the clinical syndrome is explainable by various changes in the bronchi, parenchyma or blood vessels of the lung leading to anoxemia and dysfunction of the right side of the heart —Ed]

Technic of Bronchography and a System of Bronchial Nomenclature are presented by Ralph Adams and Lowrey F Davenport[9] (Massachusetts Gen l Hosp) The materials required are illustrated in Figure 20 A

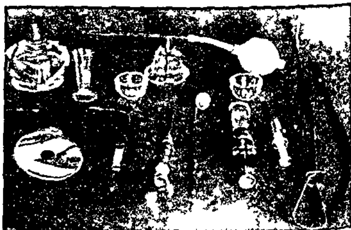


Fig 20 —Material required.

small dose of pentobarbital one hour before injection helps allay nervousness and acts as a specific prophylactic antidote to cocaine hypersensitivity Initial cocaine reaction can be promptly relieved by inhalation of amyl nitrite A dose of morphine sulfate and atropine one half hour before controls cough and decreases the amount of secretions Postural drainage accompanied by voluntary coughing and efforts to raise the sputum three hours before injection is used to empty the bronchi and facilitate the entrance of oil into the areas previously filled with secretions The oil should be introduced and the films taken in the same room A

(9) J A M A 118 111 116 J 10 194

sitting position should be used for induction of local anesthesia to the throat and tracheobronchial tree Good anesthesia is prerequisite to good bronchography The authors spray the pharynx with 3 cc of 4 per cent cocaine swab each piriform sinus and the epiglottis with 1 cc and inject 5 cc of 5 per cent larocaine into the trachea because of its lowered toxicity as compared

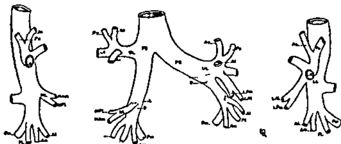


Fig 1—B h l t ee *T* t h *PB* p m ry b h *LL* pp l be b h *A* a t i fe gm t l b hu *I* l t l gmen tal bro h *As* a t p r gm t l bron h *D* d t d l segm t l b b *ML* ght m ddl l be bro h *LL* l we l b b h *Pm* post med l gm t l b h *Am* t m d l gm t l b ch *B* b l d is l b h *L* l g l d l b h *Pl* po ter l t l segm t l b h *Al* nter l t l segm nt l b h *LAl* t l t l gm t l b h f l ngul *LPm* p t rom d l seg m t l b h f l gul *MIl* pot l t l segm t l b h f h m ddl l be *MAm* a t m d l gm t l b h f ght m ddl l b *IB* t rmed t b n hus

with cocaine The method used is similar to that de scribed by Baker

Method—The urethral catheter no 16 is threaded on the metal stylet bent to an 80 degree angle 3 in from the distal end The laryngeal mirror is used and the catheter introduced into the trachea and the stylet removed The catheter should lie about 2 in above the carina and no effort is made to introduce it into the primary bronchi The patient closes his lips on the catheter and then is asked to sit on a flat topped table adjacent to an x ray tube stand where the actual injection is done A series of positions is assumed as the injection proceeds which allows gravity filling of all bron chial subdivisions The side of the chest suspected of disease should be examined first If both sides are under scrutiny it is customary to fill the left side first Four cubic centimeters

is run down the left primary bronchus into the dorsal divisional bronchus and the lower lobe segmental bronchi

One good postero anterior film will often give most of the information needed The others are necessary for confirmation The first lateral film taken defines posterior and anterior branches of the suspected side and the spatial relationships The grid film allows detailed study of areas that may be too dense to show in ordinary films such as an atelectatic left lower lobe lying behind the heart By the right anterior oblique position the left side is thrown into relief, presenting a view of the important lingula bronchus A similar portrayal of the right middle lobe is accomplished with the left anterior oblique exposure

Cases of active pulmonary tuberculosis acute lung abscess intrinsic asthma and suspected tumor should not be investigated by means of iodized oil unless exceptional reasons exist

The authors suggest a classification of tracheobronchial subdivisions designed to meet the practical needs of internists radiologists bronchologists and surgeons The diagrams pictured in Figure 21 are actual tracings from bronchograms of patients under clinical observation

[This is a useful guide to bronchography The desirability of eliminating the oil from the lungs by postural drainage immediately after roentgenograms have been made is to be emphasized otherwise the oil may be retained in the alveoli Gowar and Gilmour (*British Journal of Experimental Pathology* [illegible] 273, October 1941) describe the formation of epithelioid cells in the alveolar walls mononuclear giant cells and nodules infiltrated with lymphocytes and eosinophilic leukocytes when iodized oil (neohydriol) is retained Iodized oils seem to vary in their irritating qualities —Ed]

Bronchocinematography Its Use in Study of Bronchial Dynamics is described by M R Castex, E S Mazzei and M Malenchini[1] (Nat l Academy of Med) It affords the advantage of recording graphically at the rate of 8 to 16 times per second, the single phases

(1) Ar h a gent de enferm d ap e pir y tuberc 9 307 311 O t Nov 1941

of the respiratory cycle and of reproducing them on the cinematographic screen with slow motion By en larging the films the respiratory details and the respec tive bronchial diameters can be compared

In a previous report Castex identified two types of bronchial movements (1) passive pulsatile movements transmitted from the heart the aorta and the pulmo nary artery and from the esophagus during the act of deglutition and (2) active movements which include (*a*) alterations in length and caliber (*b*) peristaltic and undulatory movements and (*c*) torsion movements Bronchokymography facilitates the observation of the following types of movements in the normal bronchi dispersive or fanlike spread lengthening and shorten ing and inspiratory inward torsion at the level of the inferior lobes

Bronchocinematographic studies in pathologic bron chial conditions reveal the following changes In chronic bronchitis the inspiratory enlargement of the bronchial caliber is frequently absent or minimal depending on the intensity of the bronchial alteration In bronchiec tasis the lesion of the bronchial wall causes disturbance in bronchial dynamics which may lead to inversion of the normal relations i e to the diminishing of the bron chial caliber during inspiration In bronchial asthma the cinematographic findings are complex and difficult to interpret The bronchial caliber shows alterations only in those cases with coexisting old bronchial lesions In addition the iodized oil contained in the bronchi produces various images during expiration due to forced respiration and to the hypertonia of the myo elastic bronchopulmonary system According to Luis ada during forced respiration the normal inspiratory forces are operative during the inspiratory phase only with greater intensity whereas during the expiratory phase it frequently occurs that the smooth muscular fibers instead of effecting a simple tonic contraction pro duce a true wave of clonic contractions which extends

cially at night Numerous examinations since the age of 12 *gave no evidence of congenital or other heart disease* *One year* and four months prior to admission she had been hospitalized



Fig 23 —A t vi w f heart Arr w *A* h w l ter l b d f ght t l A t p th gh ght t l d t f p lm y n t p f rm d by ght t l \ t m ll f l ft t l *B* mp ed t right *A* d t k g d ff b tw right t l pp d g (d l ft *D*)

with the complaint that on the slightest exertion she had dyspnea cyanosis precordial pain without radiation dizziness and fainting spells Examination at that time revealed cyano sis widening of the heart with filling of the waist and a

markedly accentuated pulmonic second sound Largely based on the (findings and on roentgen evidence of a prominent pulmonary conus a diagnosis of congenital heart was considered Hemoglobin concentration was 122 per cent erythrocyte count 5 700 000 and leukocyte count 17,500 Sedimentation rate was 1 mm for 15 minutes and 3 mm for 45 minutes. The electrocardiogram disclosed changes indicative of pronounced right ventricular strain

On present admission there were diffuse cyanosis of the face and lips with malar flush and deep cyanosis of the nail

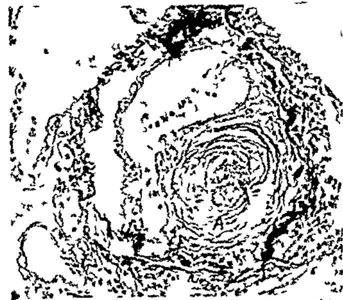


Fig 94 —Small pulmonary artery A has been seat of proliferative intimal change with a w g l lumen and a b equ nt occlusion

beds The heart appeared moderately enlarged with a strong forceful apex beat about 11 cm to the left of the midsternal line Blood pressure was 90 75 Pulmonic sound was greatly accentuated but there were no murmurs Roentgenogram of the chest showed clear lung fields moderate cardiac enlargement and extreme prominence of the pulmonary artery and conus Other findings tallied with those previously found The clinical picture was that of isolated right heart strain or cor pulmonale Absence of pulmonary conditions such as emphysema or fibrosis and of mitral stenosis which could

account for the right heart enlargement as well as absence of any tangible signs of congenital heart disease lead to diagnosis of primary pulmonary vascular sclerosis The patient died suddenly the fourth day after admission

Autopsy showed the right ventricle to be twice the size of the left ventricle and the right auricle six times the size of the left auricle Pulmonary artery and conus were extremely prominent Circumference of the pulmonary valve measured 8 5 cm that of the aortic valve 6 cm The only significant microscopic changes concerned the pulmonary vessels Most of the arterioles presented intimal proliferation which resulted in marked narrowing or occlusion of the lumen In many of them there were present thrombi of various ages Many of the capillaries were completely obliterated and hyalinized The extent of the arteriocapillary obliteration indicated a high degree of obstruction within the pulmonary circuit The larger and medium sized arteries showed no changes other than formation of occasional atherosclerotic plaques Although pathologically the coronary vessels were patent and free from sclerosis probably the final event of sudden death and the earlier attacks of precordial pain were due to acute coronary insufficiency arising from a greatly diminished volume of blood delivered to the left ventricle through the obstructed pulmonary circulation

A summary of the 19 cases of primary pulmonary vascular sclerosis previously reported in the literature is presented Diagnosis depends on two main factors (1) the demonstration (especially by roentgenographic and electrocardiographic means) of the existence of pronounced strain of the right ventricle but not of the left and (2) exclusion of all factors commonly believed to cause secondary pulmonary vascular sclerosis pulmonary hypertension or isolated strain of the right heart Several authors have stressed the importance of cyanosis in a degree out of proportion to the amount of dyspnea as a sign in favor of primary pulmonary vascular sclerosis In cor pulmonale secondary to pulmonary disease dyspnea is more apt to equal or exceed in degree the prevailing cyanosis Theories concerning etiology and pathogenesis of primary pulmonary vascular sclerosis are discussed with special reference to the possibility of an essential pulmonary hypertension

markedly accentuated pulmonic second sound Largely based on these findings and on roentgen evidence of a prominent pulmonary conus a diagnosis of congenital heart was considered Hemoglobin concentration was 122 per cent erythrocyte count 3 700 000 and leukocyte count 17 500 Sedimentation rate was 1 mm for 15 minutes and 3 mm. for 45 minutes The electrocardiogram disclosed changes indicative of pronounced right ventricular strain

On present admission there were diffuse cyanosis of the face and lips with malar flush and deep cyanosis of the nail

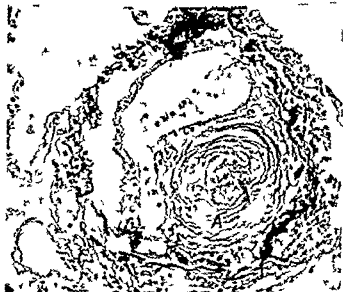


Fig 4 —Small p lm nary rtery A ha been seat f proliferati int mal hang w th na w ng f lum d a b equ nt l

bed The heart appeared moderately enlarged with a strong forceful apex beat about 11 cm to the left of the midsternal line Blood pressure was 90 75 Pulmonic sound was greatly accentuated but there were no murmurs Roentgenogram of the chest showed clear lung fields moderate cardiac enlargement and extreme prominence of the pulmonary artery and conus Other findings tallied with those previously found The clinical picture was that of isolated right heart strain or cor pulmonale Absence of pulmonary conditions such as emphysema or fibrosis and of mitral stenosis which could

sociated All patients with a low basal rate should be given thyroid pre and postoperatively Because anemia predisposes to thrombophlebitis blood transfusions and hemopoietic agents are indicated early post operatively or post partum in anemic patients before the circulatory stimulation from the operation or the delivery has passed off Varicose veins should be treated preoperatively by binding the whole affected limb tightly with elastoplast This temporarily closes off the static venous channels improving circulation in the extremities

The *most effective single procedure in preventing* venous stasis is in Ayre s opinion administration of systematic graduated postoperative and postpartum exercises as a daily routine beginning on the first day after operation The exercise should consist of lifting arms high over the head 20 times and then raising each leg the same number of times The foot of the bed should be elevated for 72 hours postoperatively then three times daily for half an hour Massage dry heat etc are also a valuable adjunct in stimulating circulation In any case in which a venous thrombosis is manifest or suspected all exercise is contraindicated and heparin should be administered

After pulmonary embolism has occurred embolectomy is a heroic procedure De Takats and Jesser advise immediate intravenous administration of atropine and papaverine (1/60 1/75 gr atropine and ½ gr papaverine) Atropine blocks the vagal impulse and papaverine acts directly on the smooth muscle of the coronaries producing relaxation It is believed that the cause of death is not the obstruction of the bronchial tree so much as the widespread radiation of autonomic reflexes Atropine and papaverine tend to prevent this spread

[Recent work on venography of the popliteal and other veins should be consulted by those interested in pulmonary embolism its treatment and prevention —Ed]

bearing a relation to the strain of the right heart analogous to the effect of essential systemic hypertension on the left side of the heart

[Hodes and Griffith (*American Journal of Roentgenology* 46 5 58 July 1941) described the roentgen appearance of the lungs in polycythemia vera and polycythemia secondary to pulmonary arteriosclerosis In the former the vascular markings may be abnormally prominent while in the latter the right heart and pulmonary conus are enlarged the middle and peripheral zones of the lung being essentially normal —Ed]

Prevention—Treatment of Choice in Pulmonary Embolism J Ernest Ayre[3] (Montreal) notes that foremost among etiologic factors in pulmonary embolism are circulatory stasis and low grade sepsis the stasis being chiefly found in the veins of the dependent extremities and pelvis Of secondary importance are surgical trauma secondary anemia hyperglycemia and dehydration Heart disease is also a factor in circulatory stasis Thrombophlebitis and embolism are much more frequent than diagnosed According to Goodall every acute pain in the chest during puerperium or subsequent to operation is embolic until proved otherwise Over 50 per cent of fatal embolism occur following pelvic operations abdominal hysterectomy especially the subtotal type, with the infected cervix left behind presenting the most hazards for thrombosis and embolism

Embolism rarely occurs during frank sepsis owing to circulatory stimulation This is true also for hyperthyroidism Taure has noted a seasonal incidence of embolism in fall and spring due to contagion of low grade sepsis which may only take the form of a cold or of subclinical attack of the flu Diabetics are prone to develop thrombosis and embolism In infected puerperium the blood sugar and lactic acid rise and the alkali reserve falls It is important that the blood sugar level be kept within normal limits during the postoperative period Obesity predisposes to thrombosis and embolism probably because of the low basal rate so frequently as

(3) Ca d M. A J 45 *43 47 S ptembe 1941

of pleurisy or pneumonia in the region of the tumor often recurrent was found in one third of the cases

Physical examination of the chest is negative until onset of complications Then the signs are those of



Fig 25—B o h l ad nom n m n, 46 B h gram h w mpl t oc l f ght l w l b b hu pool f dized ll ly g n gutte ro d growth m k a bron hu ppe t be n pped off h rply

bronchial occlusion and collapse of the lung Attacks of collapse may be recurrent probably owing to the plugging of an attenuated airway by viscid sputum which is later expectorated Complications like bron chiectasis empyema or lung ab cess may be recognized

Bronchial Adenoma A F Foster Carter[4] reports 99 cases of bronchial adenoma seen in the Brompton Hospital in a series of 453 proved cases of bronchial neoplasm an incidence of 4 8 per cent These cases are reviewed with 100 cases from the literature

Sixty two per cent of cases occurred in females. Seventy per cent gave rise to symptoms between the third and fourth decade Average age at onset was 35 Longest recorded duration of symptoms was 40 years. Average duration in all patients was five years prior to diagnosis and 87 per cent had had symptoms for a year or more The symptoms may be divided into two categories The primary features are due directly to the tumor, these are hemoptysis and cough Recurrent hemoptysis was present in 81 per cent of cases The cause is surface ulceration of the tumor with bleeding from a vascular connective tissue layer just below the epithelium Cough is at first dry and irritating and becomes productive only with onset of infection Cough was a prominent symptom in 78 per cent of cases The secondary features comprise two distinct groups (1) those due to bronchial obstruction with resulting pulmonary atelectasis and (2) those due to subsequent infection of the lung distal to occlusion Bronchial obstruction is usually gradual but occasionally a large bronchus may suddenly become occluded causing acute dyspnea and distress Dyspnea may also occur in asthmatoid like paroxysms In 31 per cent of cases dyspnea was a [illegible] and lactic acid and in 10 per cent it was [illegible] It [illegible] prominent symptom [illegible] luces sputum pain

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Fig 25—B h l d n m n m 46 B o h gr m h w mplet oc l n f right l w l be b o h p l f d d ll lyi g n gutter n d gr wth m k b n hu pp t be pped ff h rply

bronchial occlusion and collapse of the lung Attacks of collapse may be recurrent probably owing to the plugging of an attenuated airway by viscid sputum which is later expectorated Complications like bron chiectasis, empyema or lung abscess may be recognized

as such with the causal tumor remaining undetected Roentgenography of the chest is negative in the early stages Later the tumor appears as a rounded, sharply defined homogeneous shadow frequently with an area of collapse distant to it After the bronchus has become



Fig 26—Ma 47 Right lu g post m rt m polypoid t m r i m d b o hu with p tchy ul rat on f s fa

obstructed the collapse may involve the entire lobe A lateral view is essential for localizing an affected area Bronchography may reveal a filling defect or occlusion of the bronchus The shadow of a blocked bronchus is usually nipped off sharply owing to the pool of oil lying in the gutter around the growth Prognosis is good only when treatment is instituted early Delay results inevitably in bronchial obstruction pulmonary suppuration and eventual death Of the author s 22 re

ported patients 7 are dead and 15 are alive an average of 10 years after onset Seventeen deaths occurred in cases reported in the literature 10 of these were due to pulmonary infection

The most striking histologic characteristic of bronchial adenoma is the uniformity of its cells in size shape and staining properties and absence of signs of unruly growth A limited infiltration of the bronchial wall has been observed but metastatic spread is unknown and extension of the tumor is never the cause of death Although the type of cell is essentially the same in all bronchial adenomas there are distinct variations in the arrangement of cells which enable these tumors to be classified into two histologic groups Group 1 includes those tumors which have a highly differentiated structure consisting of tubules and glandular alveoli Only about one third of all bronchial adenomas belong to this type The remainder differs from the highly specialized variety only in the fact that the arrangement of cells includes both glandular and less differentiated epithelial formations The resemblance between adenomas of the bronchus and so called mixed salivary tumors is striking for both have a tendency to glandular formation of the duct to acinus type and both can exist in varying degrees of differentiation The glands of the trachea and the large bronchi are comparable to salivary glands developmentally They are composed of both serous and mucous elements and even contain crescents of Gianuzzi Therefore it seems reasonable to conclude that bronchial adenomas and benign salivary tumors are identical

The differential diagnosis between bronchial adenoma and pulmonary tuberculosis and bronchial carcinoma the two most common errors in diagnosis is discussed The following treatment is based on results obtained at the Brompton Hospital

Removal by bronchoscopic forcep is attempted first unless there are complications A radon container is then inserted

into the bronchus to treat the site of growth When bleedin is too profuse to allow removal by forceps radon is inserted to shrink the tumor and render it less vascular When this irradiation has its effect the adenoma may be removed piecemeal, and the bronchial wall once more irradiated The



F g 7 —Same c se a p e ding High powe ph tomic graph shows be n gn app a e w th a gg t n f gla d la tru t which h rs te ses le diff r t ated typ f den ma (G oup 2)

patient is studied bronchoscopically three months later, and if the tumor has recurred treatment is repeated This can be done three to four times, but not more because of danger of overdosage

Continued recurrence indicates presence of an extra bronchial extension Lobectomy is the treatment of

choice for patients with tumors which recur after bronchoscopic removal for those with large extrabronchial tumors and for those with a lung already damaged by secondary infection

[Adams Steiner and Bloch (*Surgery* 11 ›035 6 April 194?) contend that the differentiation of benign from malignant epithelial tumors of the bronchi is not possible from biopsy material alone They describe the malignant tendency of certain adenomas —Ed.]

Significance of Metastasis in Primary Carcinoma of Lungs Alton Ochsner and Michael DeBakey[6] (Tulane Univ) review the incidence of metastases to various organs and lymph nodes in a collected series of 3 047 cases Regional lymph nodes were involved in 72 2 per cent the liver in 33 3 per cent the pleura in 29 8 per cent the lungs in 23 3 per cent Next in order of frequency were bone adrenals kidneys brain pancreas peritoneum gastro intestinal tract skin spleen thyroid tonsils and tongue Of 1 298 cases in which the metastatic sites to lymph nodes were stated the tracheobronchial nodes were most frequently involved and next in frequency were the abdominal Then came the cervical retroperitoneal iliac axillary peripancreatic supraclavicular peribiliary and femoro inguinal in the order mentioned

The modes of extension of primary carcinoma of the lung are direct extension bronchial intraluminal extension implantation by aspiration biopsy or operation hematogenous and lymphatic These routes and the lymphatic drainage of the lungs are discussed in some detail The preponderance of metastases to the regional lymph nodes clearly attests to the significance of the lymphatic route

Metastasis of primary carcinoma of the lungs has a definite surgical significance The relatively high incidence of metastasis and the tendency to widespread distribution militate against increasing the incidence of operability and consequent curability On the other

(6) J Th s S g 11 1 738 Ap 1 194

hand metastasis is in some instances is late and limited to regional lymph nodes This may depend on the type of lesion and its location If the lesion is of the squamous cell variety the chances of re ectability are greater because of lesser tendency to widespread metastasis Hilar lesions are likely to metastasize later than peripherally located lesions On the basis of lymphatic drainage of the lung lobectomy should never be performed in primary carcinoma of the lung The only rational procedure is total pneumonectomy because it permits removal of both the primary tumor and the regional lymph nodes

Histories of two patients in whom metastasis developed following pneumonectomy are presented because of the interesting fact that in one the metastasis occurred in the left axillary area and the primary lesion in the left upper lobe while in the other the metastasis occurred in the right axilla although the primary lesion was in the right lower lobe The probable route of extension in both cases was assumed to be along lymphatics passing through adhesions extending from the lung to the chest wall and then traversing the chest wall to terminate in the axillary nodes

[King and Ford (*Bulletin of the Johns Hopkins Hospital* 0 1_4 156 February 1942) have presented a comprehensive study of neurologic conditions resulting from metastases in the central nervous system due to carcinoma of the lung —Ed]

Apical Form of Pulmonary Cancer Having with Pomano studied the problem of cancer of the apex of the lung for 13 years Rodolfo A Eyherabide[5] finds that this form of cancer occurs with greater frequency than generally supposed often being treated as rheumatism or neuritis Based on autopsy findings in several cases he further holds that this tumor called by Pancoast and some other American authors "superior pulmonary sulcus cancer i in reality a tumor of bronchial origin Of particular interest is the precision with which the

(5) Sema méd 48 11 9 1196 N v 13 1941

CLINICAL EVOLUTION OF CANCER OF THE THORACOPULMONARY VERTEX

S e	M st ti ns	C mments
I In tial	Den e bado v in pulmonary apex	Exclus ely radiologic stage lifficult to diagno e becau e of sim larity to apical pleuri y tomography may be of value bronchoscopy should be attempted
II Extrapuln onary invasion	Roentgen shado of pulmonary and thoracic apex plus pains in shoulder and *internal aspect of corre ponding upper* arm confirm diagnosis	*Painful thoracobrachial* syndrome of Castex Palacio and Mazzei Sympathetic disturbances may occur *In each case of pain in shoulder and* internal aspect of upper arm radiog raphy of thorax should be performed (Pancoast)
III Characteristic	*a*) Roentgen shado o er pulmonary and thoracic apex *b*) Inferior brachial paraly sis *c*) *Paralysis of the ocular sympathetic* Paralysis of other sympathetic branches (vasomot r and secretory facial disturbances) occurs Occa sionally there is phrenic paralysis alone or *with recurrent paraly is* In pical tumors localized at left ymptoms of angina pectoris may uper ene *d*) Extension of tumor into supracla vicular and *supra* and *infra pinous* fossae *e*) *Costal and vertebral osteolysis* C mpression of medulla	Sum total of radicular ympathetic and *apical symptoms* constitutes the pain ful apicocostovertebral syndrome of Tobias Anginal symptoms lead to anginal *form* of cancer of thoracopulmonary apex of Pardal
IV- Terminal		*This stage is reached if death from* inter current disease does not intervene

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(5) *Sem na méd* 48 1179 1186 Nov 13 1941

(2) those with asphyxia and (3) thos whose symptoms are the result of pulmonary fat embolism Pulmonary concussion is characterized by multiple pulmonary hemorrhages throughout both lungs usually deep in the lung substance but with no constant relation to the ribs or ramifications of the bronchial tree Rib markings can be identified only in lungs from infants or young children suggesting that the elasticity of the thorax is a factor The size of the hemorrhages is clearly related to the survival period reaching a maximum in about four hours Capillary bleeding seems to be responsible for the hemorrhages A fibrin network forms in the alveoli and a mononuclear cell exudate appears so that in 36 to 48 hours the histologic picture is strikingly reminiscent of red hepatization of lobar pneumonia The clinical manifestations of pulmonary concussion are rapid development of shock a quick thready pulse and severe expiratory dyspnea severe pain and tenderness of the trunk rapidly develop in most severe cases probably as result of intramuscular hemorrhage Restlessness may be due to subarachnoid bleeding Hemoptysis is common within an hour or so of the incident and tends to be repeated Dyspnea becomes greatly accentuated in patients dying after 36 to 48 hours and there is hemoconcentration with rise in venous blood pressure A large venesection may relieve these features Since the hemorrhages are progressive one of the main principles of treatment is immobilization of the patient as soon as possible and for several days Asphyxia may be assumed to have been the major cause of death when the air passages are found to be obstructed by powdered plaster brick dust etc or when the thorax has been compressed by a heavy mass of wood stone or metal Inhalation asphyxial lungs often show hemorrhages others show collapse and edema often more marked in one lung than the other Carbon monoxide poisoning probably the result of bursting of gas mains is a frequent complication of

disease unfolds into four distinct stages The four stages and corresponding clinical and roentgen findings are summarized in the table

[Cancer of the apex of the lung produces a maximum of neurologic symptoms and a minimum of pulmonary symptoms Early diagnosis is not easy —Ed]

TRAUMA—BLAST INJURIES WAR GASES GUNSHOT WOUNDS

Discussion on Differential Diagnosis of Lung Injuries [in War] [7] G R Cameron divides gases into two kinds (1) those like arsine which are absorbed through the lungs with few local effects and (2) those like particulates chlorine hydrogen selenide phosgene nitrous fumes, mustard gas and lewisite vapor, which act wholly or mainly on the lungs producing bronchial damage and bronchopneumonia or alveolar damage and acute pulmonary edema Bronchial damage may be caused either by the irritant gas acting on the lining epithelium with liberation of histamine like substances or through irritation of nerve endings Stimulation of the mucous glands often causes a considerable outpouring of mucus which tends to plug the bronchial cavities and cause collapse Bronchial spasm resulting from high concentration of gas may lead to acute asphyxia and interstitial emphysema Bronchial destruction is more important because of the danger of bronchopneumonia or bronchiectasis, but fortunately these complications are not common Acute pulmonary edema may lead to cyanosis and death from asphyxia If not so acute there are incapacitation and liability to cardiac failure or infection of the lungs

Geoffrey Hadfield discusses air raid casualties presenting severe respiratory symptoms without obvious surgical injury They include (1) those with pulmonary concussion without damage to the thoracic cage

(7) Lancet 1 199 Aug 16 1941

to pulmonary causes A nervous factor may be detected in cases which are apparently due to left ventricular failure or pulmonary lesions Morphine is the only drug likely to affect this condition

Archibald Fairley reports a case of phosgene poisoning and J A Ryle discusses the differential diagnosis He finds that for the experienced differentiation between blast injuries and gas poisoning should not be difficult A patient with blast injuries is ill from the start complains of pain is breathless and may have hemoptysis The symptoms of gas poisoning begin later rarely include pain or hemoptysis and there is a history of exposure to gas Rest is the first essential treatment for both The symptoms of pulmonary fat embolism may closely resemble those of phosgene gassing for they appear at about the same time and are characterized by severe pulmonary edema anoxemia and right heart failure

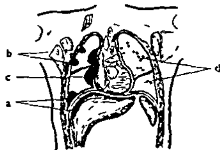


Fig 8—M[illegible] n types f h m [illegible] h g co [illegible] ss f l g[illegible]s Th ee p im ry l [illegible] n [illegible] ght d ph [illegible] ico t l [illegible] t n w th l ted l d m g b tw b m k gs n uppe l b wh h t d t [illegible] ble depth d te d t be m flu t po t rly wh they may m g t m s h l nt hila l on m p ss post ly be d ry l n d left l g m bl hem h gic spot d t h led blood ry ng [illegible] d st b t f ly f m [illegible] l be l g both lung V t [illegible] m to d p d n m t f blood t g t h nd p tu f p t t whi blood n b ch (O b [illegible])

C P G Wakeley describes a rather different type of lung injury in which the damage was certainly inflicted from without This occurred in men who had been in the water near the place where depth charges were going off Some were brought in dead others died later There was seldom extreme damage to the chest

pulmonary concussion and asphyxia Diagnosis of true fat embolism should be made only when there is a large quantity of fat in the pulmonary capillaries and there is embolism of glomerular capillaries There is usually a latent period between the incident and development of dyspnea

Shaw Dunn stresses the importance of dosage of gas in the evolution of symptoms High concentrations of phosgene elicit violent respiratory disturbance with edema and overdistention of the lungs ending fatally in a few hours lower concentrations cause early dyspnea and progressive edema which may be fatal but may respond to venesection and oxygen Bronchial spasm is an early feature but pulmonary edema is the most fundamental problem in poisoning by lung irritants Capillaries in the juxtabronchiolar alveoli show dilatation and engorgement which are greater the greater the dosage of gas The leakage of fluid into the air spaces from the capillaries may be explained by the following factors (1) slower blood flow (2) increased blood content in the capillaries applied to a greater filtering surface (3) a higher lateral blood pressure because of the greater diameter and (4) thinner walls because of distention The escape of plasma fluid is contributory to hemoconcentration and the increased viscosity of the blood accounts for the embarrassment of the pulmonary circulation Venesection which is so valuable in the treatment of blue cyanosis in gassing is hardly helpful in the stage of gray cyanosis when peripheral circulatory collapse has already set in

G R Osborn outlines his experience with primary secondary and reactionary lung lesions resulting from a bomb explosion The primary and secondary lesions are illustrated in Figure 28 Reactionary lesions are principally acute pulmonary edema pseudopneumonia and true pneumonia Pulmonary edema is divided into three groups (1) that primarily due to brain lesion (2) that due to left ventricular failure and (3) that due

capillary bed is reduced and the danger of a rise in pulmonary arterial pressure and of pulmonary edema as a result of increased venous return is made greater

There is usually a prolonged and great increase in respiratory rate of rabbits which survive exposure to blast apparently due to stimulation of deflation endings and increased sensitivity of stretch endings to expansion of the lungs not to chemical changes affecting

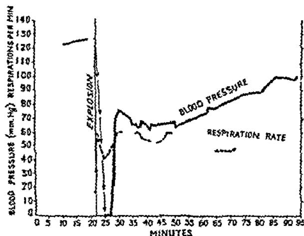


Fig 9—Blood pressure and r p ti n sta f r bb t wh h surv ed ex posur to p u e w ll bo l l t whi h 50 pe ent of xposed but u p otected rabbits will be immed at ly killed as r sult of l l n

the respiratory center or to a direct effect of the blast on the medulla When the lung is so severely damaged that whole lobes are consolidated respiration is labored because of the changes in the elastic recoil of the lungs Animals exposed to high blast pressure show no concussion as demonstrated by electrocorticogram recordings Immediate death unassociated with external trauma appears to be due to shock following internal injury This condition is occasionally associated with occlusion of the larger air passages by blood clots De

They complained of abdominal pain and often had hemoptysis hematemesis and diarrhea Autopsy showed the appearance of blast injuries to the lungs ruptured liver and other abdominal traumas

Physiologic Effects of Blast P L Krohn D Whitteridge and S Zuckerman[8] (Univ of Oxford) exposed animals to a charge of 8 to 33 lb polar ammon gelignite from a distance of 6 to 14½ ft The results of the experiments are summarized

A series of experiments in which rabbits trunks were protected while their heads were directly exposed to high blast pressures brought final confirmation to earlier observations that thoracic and abdominal blast injuries are due to the impact of the pressure component of the wave on the body wall and not to either the pressure or the suction component acting through the nose and mouth It may occur when the suction component is excluded

Electrocardiographic records show that there is no lack of coordination of the heart beat in blasted animals The electrocardiogram of animals which survive exposure to high blast pressures may show evidence of a transitory phase of anoxemia Slight slowing of the heart rate occurs in anesthetized animals which survive whereas the rate in unanesthetized animals is frequently accelerated There is an immediate fall in arterial blood pressure which in extent and duration is related to the peak blast pressure experienced There is a slight maintained fall as found by Hooker in venous pressure These shock symptoms are not due to vagal inhibition While the fall in pressure can be regarded as being partly a shock effect of pulmonary and extrapulmonary trauma the change in systemic blood pressure is chiefly secondary to changes in the pulmonary blood flow The condition of the pulmonary circulation in severely blasted animals resembles that in animals given intravenous injections of starch In both the extent of the reserve

(8) Lancet 1 5 58 Feb 28 194

rhages were found. Rigidity of the abdominal wall was probably caused by irritation of the intercostal nerves by the extrapleural hemorrhages. Free hemoptysis was observed in only two patients and was not a prominent clinical feature. Cough when present usually appeared 24 hours after the injury. Restlessness was a constant symptom and bore a direct relation to the severity of the condition. Ruptured ear drums were common and purulent otorrhea occurred in a few instances.

On physical examination the chest was seen to be held about three quarters expanded. The percussion note was resonant in all areas in the early stages. Coarse râles were heard over the whole lung and persisted longest at the bases. A striking feature was the development of clinical signs of lobar pneumonia at the lung base. The correct explanation is that these signs are largely due to the effusion of blood which corresponds roughly to the stage of red hepatization of lobar pneumonia and may be expected to give rise to the same physical signs. Roentgenograms of the chest showed the heavy mottling over large lung areas characteristic of severe blast injury (Figs. 30 and 31).



Fig. 30.—Tw[illegible]

At autopsy the most striking feature was effusion of blood which varied in different cases from capillary

layed death usually is due to pulmonary edema more rarely it may be due to intraperitoneal hemorrhage

In man a moderate or severe degree of pulmonary blast injury may be associated with symptoms of tightness in the chest difficulty in deep breathing and the feeling of having been kicked in the stomach These symptoms are related to an overactive Hering Breuer reflex In presence of other injuries they may be inconspicuous and diagnosis depends on an accurate history of the circumstances of the injury and the state of the ear drum and middle ear Experimental experience indicates that rapid shallow breathing or slow labored breathing is to be expected Treatment should be directed toward avoiding overtaxing an already diminished pulmonary capillary reserve Oxygen, morphine and venesection may be beneficial transfusion general anesthesia and exertion are contraindicated

Blast Injury of the Lungs J N O Reilly and S Roodhouse Gloyne[9] (St Margaret s Emergency Hosp London) report observations on 17 victims of a nearby blast from a high explosive bomb Ten had a severe blast injury to the lungs—eight without external chest injury and 2 with external injury to the chest, 7 had less severe blast injury Shock was profound in the severe cases and was invariably present in the others Dyspnea was a constant sign it was due partly to pain and partly to extreme bulging of the chest which appeared to be in a position of almost full inspiration Cyanosis was marked in severe cases and present in all Pain occurred in two distinguishable types as deep central pain which was probably related to mediastinal hemorrhages and as less severe lateral pain possibly caused by contusion of intercostal muscles aggravated by breathing Pain in the abdomen was an important feature in five cases In two patients the appearance simulated an acute abdominal condition and a laparotomy was performed but only a few subserous hemor

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the war gases also contain more potent polarizing radicles like oxygen sulfur arsenic a nitro group or oxime which may be relatively hydrophilic or which may reduce the strength of the halogen bond

In the biologic effects of war gases therefore one or more of the following factors are concerned (1) relative water fat and protein solubility both in transport and in relation to cell surface (2) relative ease of hydrolysis with relation to possible formation of halogen acid and the effects of the rest of the molecule (3) distortion of cellular surfaces due to molecular configuration of war gas molecules or to their secondary valence forces and (4) effects of war gas molecules on pH redox potential and colloid interface and enzyme equilibriums

Absorption of the ordinary was gases and their many obvious chemical relatives may be inhibited by neutralizing hydrolysis oxidation or adsorption For civilian use these methods may be improvised from material available at homes The most readily available effective oxidants are the common kitchen bleach solutions such as Clorox These are buffered 3 5 per cent sodium hypochlorite solutions and are nonirritating for blotting the skin but should be diluted for application to mucous membranes for washing the skin or for wetting cloths through which to breathe Such a solution reacts promptly with mustard gas 2 2 dichlorodiethyl sulfide converting it quantitatively to the nontoxic crystalline 2 2 dichlorodiethyl sulfoxide For alkaline hydrolysis sodium bicarbonate solution about 2 per cent may be readily prepared by dissolving 1 teaspoonful of baking soda in a glass of water Such a solution is helpful in washing out the eyes nose and throat in suspected war gas irritation or for wetting cloths through which to breathe The most suitable and readily available detergent adsorbent is lather from ordinary soap or soap flakes and water or tincture of green soap This is particularly useful as are hypochlorite solutions in pre

oozing to large hemorrhages Histologically the chief findings were (1) extensive outpouring of erythrocytes (2) rupture of elastic tissue and capillaries and (3) secondary infection with streptococci and bronchopneumonia No evidence of fat embolism was found

Treatment consisted of treating shock with morphine and heat continuous oxygen in severe cases transfusion of plasma (blood transfusion was given only for concomitant hemorrhage) and sulfapyridine prophylaxis Rest is of prime importance anesthetics are contraindicated



Fig 31—Small pn m thorax at l ft ba with m ttl g of l ft lung f ld (O Re lly Gl yne)

Mechanism of Action of Ordinary War Gases is discussed by Chauncey D Leake and David F Marsh[1] (Univ of California) The ordinary war gases may be considered to be chemical relatives of such types of aliphatic hypnotic and inhalation anesthetic agents as alcohol chloroform and ether (see Table) There is general knowledge of the locally irritating powers of these compounds Their war gas relatives may owe an increased irritative action to aggressive factors associated with altered halogenation and polarity These war gases usually contain a rather labile halogen like chlorine or bromine which with the hydrocarbon portion may be considered to be relatively lipoproteophilic with respect to the rest of the molecule On the other hand

(1) S i 96 194 197 A g 8 194

the war gases also contain more potent polarizing radicles like oxygen sulfur arsenic a nitro group or oxime which may be relatively hydrophilic or which may reduce the strength of the halogen bond

In the biologic effects of war gases therefore one or more of the following factors are concerned (1) relative water fat and protein solubility both in transport and in relation to cell surface (2) relative ease of hydrolysis with relation to possible formation of halogen acid and the effects of the rest of the molecule (3) distortion of cellular surfaces due to molecular configuration of war gas molecules or to their secondary valence forces and (4) effects of war gas molecules on pH redox potential and colloid interface and enzyme equilibriums

Absorption of the ordinary was gases and their many obvious chemical relatives may be inhibited by neutralizing hydrolysis oxidation or adsorption For civilian use these methods may be improvised from material available at homes The most readily available effective oxidants are the common kitchen bleach solutions such as Clorox. These are buffered 3 5 per cent sodium hypochlorite solutions and are nonirritating for blotting the skin but should be diluted for application to mucous membranes for washing the skin or for wetting cloths through which to breathe Such a solution reacts promptly with mustard gas 2 2 dichlorodiethyl sulfide converting it quantitatively to the nontoxic crystalline 2 2 dichlorodiethyl sulfoxide For alkaline hydrolysis sodium bicarbonate solution about 2 per cent may be readily prepared by dissolving 1 teaspoonful of baking soda in a *glass of water Such a solution is helpful in* washing out the eyes nose and throat in suspected war gas irritation or for wetting cloths through which to breathe The most suitable and readily available detergent adsorbent is lather from ordinary soap or soap flakes and water or tincture of green soap This is particularly useful *as are hypochlorite solutions in pre*

venting skin injury from contact with blister gases

CHEMICAL RELATION BETWEEN COMMON IRRITANT DRUGS AND TYPICAL WAR GASES

[illegible]	CORRESPONDING WAR GAS
[illegible] H CH CH OH	Ethyl dichloroarsine H-CH CH - AsCl$_2$
Chloroform Cl C H	Chloropicrin Cl C NO
Ether H CH CH O	Mustard gas (Cl-CH CH) S

Bronchoscopic Investigation and Treatment of Experimental Phosgene Poisoning in Goats are reported by John F C M Cobb n Twelve goats were exposed to phosgene gas and six of the animals were examined and treated bronchoscopically Six were left untreated as controls Duration of exposure varied from 10 to 20 minutes and concentration of gas from 1 11 000 to 1 4 000 The six treated animals were subjected to one bronchoscopic aspiration and insufflation at 4½ to 7 hours after exposure and two of them were treated a second time after 12 hours Each operation continued for 10 minutes and during that time a mixture of 95 per cent oxygen and 5 per cent carbon dioxide was allowed to flow 1 will the bronchoscope at the rate of 1 l per minute Of the six treated animals four survived for three days when they were killed while of the untreated animal only two survived for that length of time

Study of pathological changes through the bronchoscope and at autopsy showed that inhalation of phosgene gas produces an acute inflammatory reaction of the epithelium of the respiratory unit and of the mucous membrane of the trachea bronchi and bronchioles Two distinct types of free fluid are produced in the lower respiratory tract during life as a result of exposure to phosgene gas (1) an abundant clear non

( ) Tate 1 3 52 71 M 5 124

coagulable edema fluid poured out into the spaces of the *respiratory unit (the interstitial tissue of the* interlobular planes subpleural tissue and alveolar walls) (2) thick viscid semicoagulable mucus excreted into the airways. The common finding at autopsy was a *variable degree of consolidation of the lungs. The* similarity of lung changes in phosgene poisoning to those seen in other pulmonary conditions such as the effects of bronchial foreign body drowned lung pneumonia lung changes secondary to simple and malignant neoplasms *pneumonitis and unresolved pneumonia* leads to the assumption that following inhalation of phosgene gas the increased mucus forms plugs in the small bronchi and bronchioles thus preventing removal of the free *edema fluid from the more distally situated respiratory* spaces. Thus the undrained portion of the lung becomes consolidated. The obstructive agent in phosgene poisoning differs from that in respiratory poisoning *by chlorine and blistering gases in which obstruction* is caused by shed and necrotic mucous membrane.

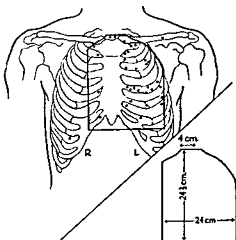
The rationale of bronchoscopic treatment is that removal of mucous secretion from the tertiary and smaller *bronchi will prevent the damming back of edema fluid* and consequent consolidation. This is suggested only as auxiliary treatment and not to replace the presently recognized therapeutic measures for phosgene poisoning.

Comparison of Course and Direction of Fatal and Nonfatal Gunshot Wounds of the Chest. Harry C Hardt Jr and Lyndon Seed[4] (Univ of Illinois) studied coroners reports of 100 consecutive cases of gunshot wounds of the chest in which the injured lived less than 12 hours and records of 100 patients who recovered from penetrating chest wounds. Postmortem records indicated hemorrhage as a constant finding. Hemothorax was present in 95 cases; the heart or great blood vessels were penetrated in 85 cases; *hemopericardium* was present in every case in which the pericardial sac was

(4) W Med 6 3 634 3 1 194

pierced in 10 cases there were large mediastinal hematomas In all cases in which the lungs were pierced an area of hemorrhage surrounded the track of the bullet in some of these hemorrhage was considerable and not confined to the area immediately surrounding the track

Most of the wounds of entrance in both fatal and non fatal injuries were located on the anterior aspect of the chest In nonfatal cases the distribution was fairly even except that the precordium was not involved In fatal cases most entrance wounds were on the left anterior aspect and only a few were slightly to the right of the midline In the most superior cross section of the chest of the series of fatal wounds all of the projectiles took a fairly direct course in the anterior posterior axis converging near the midportion of the mediastinum In the lower portion of the chest more of the projectiles were directed at a slight angle passing from the left side of the anterior aspect of the chest to the right side of the posterior aspect A few passed from one axilla to the opposite one but all the paths tended to cross in the cardiac area in the anterior portion of the chest on the left side In nonfatal injuries the paths of the projectiles had no distinctive pattern except that the mediastinum was rarely involved



F g 3 —P ts f ent a e on a t as pect of ch t f p j t l c g fatal gun h t w nd P t t by a mo is gg st d for ar outl ed o d g t shap s d d m s fo he t f ge s

In modern warfare because severe gunshot wounds of the chest tend to be rapidly fatal it is increasingly important to consider the possibility of preventing these wounds As seen in Figure 32 in the series of fatal wounds protection of the indicated area would have prevented 63 of 66 wounds of the anterior part of the chest and 6 wounds of the anterior axillary portion of the chest on the left Armor made of lighter material which is now available in the indicated dimensions would have only a fraction of weight of the present armor and would interfere with activity only slightly

DISEASES OF THE PLEURA

Diagnostic and Prognostic Value of Estimations of Free Sugar in Pleural Effusions is discussed by E Nassau[4] Hagedorn and Jensen's method was used for the sugar determinations and the pleural fluids were examined immediately after aspiration to avoid possible glycolysis Pleural fluids from 14 patients with exudative pleurisy fluids from 43 patients with effusions complicating artificial pneumothorax and empyema fluids from 5 patients with tuberculous empyemas following pneumothorax effusions were examined Of the 14 pleural fluids 8 showed tubercle bacilli on culture Average sugar content in these eight was 49 25 mg per cent the lowest value being 15 and the highest 84 mg per cent Average sugar content of the culture negative fluids was 115 16 mg per cent with the lowest value 80 and the highest 132 mg per cent Average duration of the effusion before the first examination in this group was 27 days Positive cultures were obtained in 17 of the 43 fluids Average sugar content of these was 40 29 mg per cent the lowest value being 4 and the highest 92 mg per cent Average duration of the effusion at the first examination was seven days The corresponding

(4) Tubercle 23 249 251 October 1942

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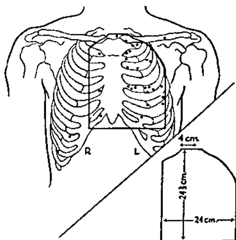


Fig 3 —P nta f t e on a t as- p t f h t f p j t l u g fat l gu hot wou d I te t n hy m s gg ted f rea tl ed d g t h p a d d m f he t f ave ge i

tion required In this group there were 23 pneumococcic and 5 hemolytic streptococcus cases and in 1 case no growth was obtained

In the other series were 30 unselected cases of empyema which occurred during or after sulfonamide treated pneumonias In four cases the empyema was interlobar in type in three encapsulated in two posterior with an associated independent interlobar pocket and in one it consisted of a small encapsulated pocket in the vertebral gutter In nine there was marked delay in the reexpansion of the lung and in two it was necessary to do secondary drainage operations There were two deaths in this group one due to toxic hepatitis from sulfathiazole and one to brain abscess There were 25 pneumococcic 3 hemolytic streptococcus and 2 hemolytic staphylococcus cases

A review of the literature shows a reduction in the incidence of empyema since introduction of sulfonamide therapy in the pneumonias from 5 to 1 per cent or less However when empyema does occur it is apt to be atypical and more difficult to treat satisfactorily The authors believe that once pneumonia has been adequately controlled and certainly when pus has been demonstrated in the pleural cavity sulfonamide therapy should be discontinued Two of the most valuable clinical guideposts in treatment of empyema are the fever curve and appetite Where drainage has been adequate the temperature returns promptly to normal and the appetite becomes good Conversely when drainage has been inadequate there are a prompt rise in temperature and an associated anorexia Sulfonamides which are known for their antipyretic properties and their anorexic effect may obscure the picture and render proper surgical procedure difficult

[Certain reports have suggested that sulfanilamide tended to attain a high concentration in the pleural exudate However Janeway (*Archives of Internal Medicine* 69 May 194) points to a technical error in estimating the concentration False readings are due to the fact that procaine hydrochloride injected

figures for the culture negative fluids were average sugar content 88 5 mg per cent lowest value 63 m and highest value 136 mg Average duration was 1? days The empyema fluids showed a uniformly low sugar content average being 12 4 mg highest value 22 mg and lowest value 7 mg per cent Average duration of the empyema was 45 days

Subsequent examinations were carried out in 6 of the 26 abacillary pneumothorax effusions the remainder having absorbed and in 11 of the 17 bacillary effusions the latest reexamination of an abacillary effusion was made in 35 days and of a bacillary effusion in 183 days Subsequent examinations in the abacillary group showed results similar to those obtained on first examination Of the subsequently reexamined 11 bacillary effusions nine showed lower figures one remained unchanged and one showed a slight increase The empyema fluids reexamined at various intervals up to eight months from the first examination also gave low sugar values

From these results Nassau concludes that a high sugar content of a pleural effusion generally over 70 mg per cent is a prognostically favorable sign indicating that the effusion is in all probability sterile or if containing tubercle bacilli that absorption may be expected within a reasonable time A low sugar content under 50 m per cent almost invariably indicates presence of tubercle bacilli in the effusion and absorption is usually delayed or empyema may ensue

Influence of Sulfonamide Therapy on Postpneumonic Empyema Thoracis was studied by Thomas H Bufford and Brian Blades (Washington Univ) Two series of cases were compared One included 29 unselected cases of postpneumonic empyema not treated with any of the sulfonamides All were general in type except one which was interlobar Prompt recovery occurred in all and in no instance was there any delay in obliteration of the pocket In no case was a second drainage opera

(5) J A M A 118 J 0 J M 1 194

and mediastinum and lungs become fixed Purulence is a late characteristic of the exudate and is thought to synchronize with recession of the acute pneumonic process Early aspiration to relieve pressure is indicated Drainage should be done when frank pus is demonstrated that is when the acute process has subsided and the lung well supported by adhesions is protected against a disastrous bilateral collapse By the proper timing of rib resection for drainage and by early and consistent instillations of Dakin s solution as advocated by Graham for sterilization of the cavity mobilization of the lung and obliteration of the cavity a high mortality rate and much morbidity are avoided

The rule applied to pneumococcic empyema is used in Bacillus coli empyema

Putrid Empyema Herbert C Maier and Edwin J Grace[7] state that anaerobic or putrid empyema may be clinically differentiated from the aerobic type by the presence of a foul offensive odor of the purulent fluid During two years 23 cases of putrid empyema were treated in the Kings County Hospital Brooklyn exclusive of those following surgical intervention in the thorax The sixth decade of life was most frequently represented 87 per cent of the patients were males and 13 per cent females In every case in which anaerobic cultures were made anaerobes were demonstrated in the pus streptococcus the hemolytic type prevailing over the nonhemolytic being the most frequent organism encountered in both aerobic and anaerobic cultures Staphylococcus aureus was likewise frequently found in both cultures

Most patients gave a history of sudden onset to the acute illness Chest pain was present in most at some time Twenty patients had a cough 13 of them of a productive kind Five had foul sputum and in each of these there was either an associated pulmonary abscess of appreciable size or a bronchopleural fistula Pre

(7) S g Gy & Ob t 74 69 74 J y 194

to anesthetize the pleura prior to aspirating the fluid gives a color reaction similar to that of sulfanilamide when using the method of Marshall Emerson and Cutting —Ed]

Acute Empyema is reviewed by J R Nugent[6] (St John N B) Bacteriologically and etiologically there are three types of empyema (1) pneumococcic associated with lobar pneumonia, the infection reaching the pleura through rupture of a localized lung abscess (2) streptococcic due to hemolytic streptococcus and associated with the pneumonias of scarlet fever influenza and measles with blood borne infections from tonsils, mastoids etc or with direct infection from chest wounds and (3) Bacillus coli empyema arising in association with the peritonitis of suppurative appendicitis perforated peptic ulcer abscess of the liver, subphrenic abscess and suppurative pelvic disease the infection in Nugent s opinion being carried to the mediastinum by the lymphatics draining the paracolic gutter

Pathologically the empyemas fall into two main types pneumococcic and streptococcic which differ fundamentally from each other The pneumococcic types develop late in the course of pneumonia, usually after crisis has been reached and resolution begun The effusion is diffuse purulent slow to organize and to form adhesions it does not produce pleural thickening Rib resection for early open free drainage on diagnosis is accepted as standard treatment

In streptococcic empyema the effusion develops early in pneumonia and may be present before pneumonia is manifest Both pneumonia and effusion form a single clinical picture The parenchyma of the lungs is fixed by engorgement the bronchioles are plugged with a thick fibrinous exudate and multiple small abscesses form The mediastinum is pushed over by the effusion the lung root distorted and the circulation embarrassed The patient is dyspneic livid-cyanotic and hoarse Both pleural surfaces become thickened adhesions are formed

(6) Canad M A J 46 357 360 April, 1942

Texas) on the basis of a critical study of 33 cases In most of the cases the cause of chronicity was obvious In many the presence of pus in the pleural cavity had not been recognized until a spontaneous sinus or a bronchial fistula occurred In others in which the acute infection was diagnosed a drain had been inserted and left out after a few days or a few weeks That efficient and continuous drainage is the greatest single measure in avoiding chronicity is shown by a summary of 172 consecutive cases of acute empyema treated with closed intercostal drainage only 6 of which became chronic

Nonoperative measures include vaccine therapy Beck s paste and high vacuum suction The first two have long since fallen into disrepute and the third may be effective in long standing thick walled cavities but troublesome hemorrhages may occur from the granulations present if the negative pressure is great

While in most instances a more formidable operative procedure is necessary preliminary adequate drainage leads to a diminution in the size of the cavity and by preventing the pus to accumulate relieves sepsis In a number of cases this alone accomplished cure In using any of the operative procedures efforts have been made to avoid deformity especially in growing children Thoracoplasty seems on the first glance to be the most deforming operation However in long standing empyema a collapse of the chest has already occurred on the affected side and is often accompanied by scoliosis with its concavity toward this side In many of the authors cases the empyema was of such long duration (4 12 years) that the chest was already hopelessly deformed so that further deformity from thoracoplasty was not serious

Extensive one stage operation involving wide opening of large cavities and decortication was found in some instances to lead to dangerous hemorrhages Multiple stage rib resection has become the choice in chronic empyema because of its safety and success After each

liminary diagnosis of pneumonia was made in most cases Diagnosis of putrid empyema was definitely established by aspiration of foul pus or foul air from the pleural cavity Delay in diagnosis may be due to interior location of the empyema Low aspiration may be dangerous because of the possible elevation of the diaphragm as result of previous intrapulmonary disease

Open thoracotomy with rib resection should be performed as soon as the diagnosis is confirmed by aspiration Thoracocentesis is associated in these cases with considerable danger of chest wall infection Thoracotomy was performed in 22 patients One patient died of diabetic acidosis before the pleural cavity could be drained within a few hours after a phlegmon of the chest wall which developed as result of thoracocentesis was drained Half the patients were operated on within 24 hours after the first aspiration Eighteen had only a single aspiration Two were aspirated more than twice before thoracotomy both patients died

With early operation prognosis is good as far as the pleural infection is concerned The most important factor in prognosis is the presence of an extensive intrapulmonary suppuration Oxygen therapy should be used freely Zinc peroxide packing should be inserted into the thoracic wall wound to prevent necrosis Drainage should be prolonged in presence of a bronchopleural fistula The sulfonamides are of benefit in some cases but lack the usual dramatic response Painful swollen joints were present postoperatively in several of the cases Due to slow subsidence of the intrapulmonary infection several patients continued to be febrile for almost a month after operation and four patients for six to seven weeks All 20 patients who recovered obliterated the empyema cavity after thoracotomy and the wounds healed

Chronic Nontuberculous Empyema is discussed by Albert O Singleton and Robert M Moore[8] (Univ of

(8) J Th a c S rg 11 169 186 De mb

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sta_e the periosteal beds of the resected ribs are treated with formalin A sufficient number of ribs and a sufficient length of each rib must be removed The total resection should extend one segment above and one segment below the cavity When the cavity extends beneath the posterior angles of the ribs the posterior ends of the ribs should be removed completely This procedure has been particularly effective in children and much of the hemorrhage and shock has thus been avoided Adults with long standing cavities especially when the cavities are large and one wall is formed by the mediastinum or pericardium present added difficulties In these cases various modifications of the Schede Estlander or Fowler Delorme operation have been used Muscle implantation is one of the most popular methods In extremely difficult cases the authors have succeeded in some instances by unroofing the cavity saucerizing

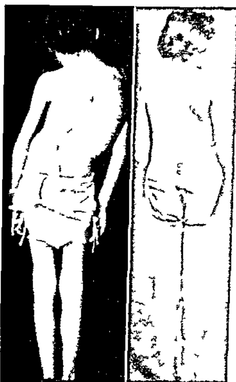


Fig 33 (left) —Ma k d lat l curvatu re ult of empyem u mm n curr ce
Fig 34 (right) —Ch mpy m of ev yea s dn t n w th t l t l curv tu

it as much as possible and sliding into the cavity a long musculocutaneous flap sutured to the deepest portion of the cavity the more shallow portions being left uncovered to epithelialize

Twenty three patients were cured six died (two died of cardiac complications one committed suicide one died from surgical shock and two were small children admitted in extremis) in four the cavity still drains

Chylothorax Peport of Case Arrested by Phrenicotomy Chylothorax is rare there being 84 cases reported up to 1937 It is usually found on the right side but may occur on the left particularly in injuries to the cervical or upper thoracic portions of the duct it may be bilateral or associated with chylopericardium and chyloperitoneum The chief cause is trauma of open or closed type In the latter fractures of vertebrae or ribs play an important part Hyperextension of the spine is an important mechanism in production of thoracic duct injuries Other etiologic factors are new growth and granulomas thrombosis of the left subclavian vein perforating lymphangitis aneurysm of the duct hepatic cirrhosis and filaria Spontaneous rupture is possible Special symptoms of traumatic chylothorax (Mouchet) are (1) delay in onset of 2 to 40 days (2) collapse or shock caused by change in intrathoracic pressure (3) inanition oliguria and thirst which may be present even after intravenous reinfusion of aspirated chyle Pseudochylothorax empyema tuberculosis calcareous effusion and thoracic tumors present clinical pictures similar to chylothorax Diagnosis is established by aspiration of chyle Treatment consists of aspiration and intravenous reinfusion When chylothorax is caused by injuries to the neck—fracture of the clavicle with compression of the subclavian vein—correction of clavicular deformity is indicated

Stanley J G Nowak and Preston N Barton[9] (Boston City Hosp) report a case

(9) J Thor c S g 10 6 8 634 A gust, 1941

Man 56 complained of constant nonradiating midepigastric pain cough and moderate dyspnea on exertion of three to four months duration He lost 18 lb Recently he had received numerous injections presumably for syphilis The pertinent physical findings were moderate emaciation signs of fluid in the lower half of the right side of the chest presystolic and blowing systolic murmurs at the apex blood pressure of 130/5 in the right arm and 95/50 in the left and capillary pulsation in the finger tip There was no alteration in the lymphocytic and eosinophilic elements in the blood Kahn and Wassermann reactions were positive Thoracocentesis yielded milky fluid Fluoroscopy immediately after aspiration showed lessened aeration of the right lung and flattening and limited excursion of the right side of the diaphragm There was a questionable tumor in the right mediastinum Roentgenograms showed diffuse mottling of the entire right side of the chest most marked at the apex Repeated aspirations during the following eight months and *pneumothorax failed to prevent reaccumulation of chylous* fluid Administration of scharlach R orally resulted in its appearance in the chylous fluid the next day After phrenicotomy under local anesthesia the symptoms caused by chylothorax were completely relieved The patient died of cardiac failure 10 months later Autopsy showed the right pleural cavity to be almost completely obliterated by adhesions of the visceral and parietal pleurae At the level of the eighth thoracic vertebra there was a small opening in the thoracic duct The aorta showed tree bark roughening

In the absence of common etiologic factors in this case the possibility of spontaneous or syphilitic perforation was considered Syphilitic perforation cannot be invoked in the absence of definite syphilitic pathology in the thoracic duct

The early roentgen appearance of a tumor in the right posterior mediastinum emphasizes a point concerning the early manifestation of the disease which the authors have termed retropleural chyloma Although the shadow is not specific for the condition such a shadow occurring with a history of trauma several days to several months previously should suggest the possibility of perforation of the duct *At this stage diagnostic* aspiration should be carried out followed by thoracot

omy and extrapleural drainage which should be done in order to prevent intrapleural extravasation

The mechanism by which phrenicotomy favors healing of low thoracic duct perforations is presumably due to elongation and narrowing of the crural sulcus with apposition of the diaphragmatic and mediastinal parietal pleurae Other mechanisms such as elimination or diminution of the aspirating action on the open thoracic duct of the respiratory movements and clot formation of lymph due to elimination of the defibrinating action ascribed to respiratory movements may also operate

[Little Harrison and Blalock (S rgery 11 9 401 March 194) present a study of chyloth rax and chyloperitoneum and lscu the effect of the fat f e d et and of reinjection of the aspirated chyle —Ed]

CHEST WALL AND DIAPHRAGM

Treatment of So Called Idiopathic Spontaneous Pneumothorax is described by A Brunner[1] (Univ of Zurich) Treatment has two objectives (1) to relieve tension pneumothorax and (2) to insure closure of the pulmonary fistula In tension pneumothorax rapid removal of air may become an emergency measure Any hollow aspiration needle can be inserted through the first or second intercostal space anteriorly so as not to move the patient The air escapes with a noticeable hiss following which the needle is withdrawn If however dyspnea soon returns the needle may have to be reinserted It is then best provided at its outer end with a rubber finger cot which has a small hole in its center and acts as a valve letting the air out but not in In presence of a widely gaping pleuropulmonary fistula this valve drainage may have to be continued for some time and there is danger that the sharp point of the needle may injure the lung during forceful expiration or cough In such cases instead of the needle a narrow

(1) S hw m d W h h 71 1 101 1 O t 18 1941

catheter (10 12 Charrière s) is introduced through the same space by means of a trocar, the catheter is connected with rubber tubing which has a finger-cot valve at its *lower* end and is immersed in water (Fig 35)

When the nontuberculous spontaneous pneumothorax is associated with moderate dyspnea the intrapleural pressure is regulated by the pneumothorax apparatus. The pressure is regulated at slightly positive values, e g + 1 + 3 cm water When markedly increased pressure prevails the excessive air is removed with the pneumothorax apparatus If an apparatus is not available an inserted aspiration needle is left open and the air made to escape until the attached manometer indicates the desired pressure Creation of a marked negative pressure should be strictly avoided during the first few days, lest with each inspiration the air will again escape from the lung through the fistula On the other hand when the fistula remains closed for a few days it may become obliterated and thus promote spontaneous cure of the pneumothorax The intrapleural pressure should be controlled often and if within a week the pressure is not increased but even diminished owing to resorption of air it can be surmised that the fistula is closed Unlike in artificial pneumothorax there is no objection to repeated withdrawal of air to promote rapid reduction in size of the pneumothorax

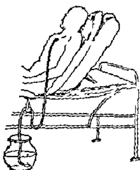


Fig 35 —Continuous equalization of pressure in tension pneumothorax

In many instances the fistula has to be closed artificially Thoracoscopy is valuable When the lung is maintained partly expanded by strands of pleural adhesions cauterization of the adhesions will bring about complete collapse of the lung and thus closure of the fistula Figure 36 shows the endoscopic picture of an

emphysematous bleb of the size of a hazelnut with a small tear which was kept expanded by strands of adhesions Following cauterization of these strands the bleb collapsed and the pneumothorax was slowly resorbed When no adhesions are seen in the vicinity of the bleb the wall of the bleb itself is cauterized When the fistula cannot be located with the endoscope or when the endoscopic treatment has not been successful there



Fig 36 —Thor scop fi d ngs n po t neo pn umoth mphy m t u bl b Lung is fi ed t thor wall by dł ns, with n wb h li f h lnut

remains as a last resort the artificial production of a pleural exudate by injecting 50 cc of a 50 per cent dextrose solution The injection may be repeated after a two days interval and 100-125 cc of the solution used

[The thoracoscopic approach to better diagnosis of the cause of this condition and its treatment is winning increasing favor particularly when the tension of an adhesion prevents the healing of the pleural fistula —Ed]

Uncomplicated Fractures of Ribs and Major Injuries of Chest Wall Treatment by Infiltration with Local Anesthetic is reported by Paul H Harmon Dan F Baker and Robert D Kornegay (Sayre, Pa) Thirty two patients with minor fractures of ribs and five with major thoracic injuries were treated The local anesthetic consists of a double solution containing 0 5 per cent procaine hydrochloride and 0 1 per cent eucupine dihydrochloride to which epinephrine hydrochloride (10 drops per 100 cc) is added Multiple fractures extensive injuries of the thoracic wall, mild or moderate shock and presence of emphysema instead of being contraindications are indications for use of the method

PROCEDURE —After diagnosis is made and the site of fracture accurately localized by roentgenograms the patient is placed on a table and a mark is made with solution of gentian violet or silver nitrate stick A wheal is raised over the proposed site of injection 1 cc solution is placed deeply in the subcutaneous tissues and 2 3 cc solution infiltrated directly into the site of fracture If this site and its surrounding hematoma cannot be directly entered or identified with the tip of the needle 4 6 cc solution is placed in the surrounding tissues A small gauze dressing or a small cotton or gauze pledget soaked with collodion serves as a temporary dressing The primary anesthesia obtained with the anesthetic solution lasts three to four hours

Often one injection suffices In 8 of the 32 cases of minor fractures a second injection was necessary but in no instance was a third injection necessary Average period of disability was 4 2 days Twelve patients with fractures of a single rib returned to work immediately after treatment The 32 patients were given entirely ambulatory treatment All of the five patients with major injuries derived comfort from the injection treatment and in one instance the method was considered life saving since the clinical picture shifted after use of the solution

The method eliminates rib strapping and sedatives

(J A M A 116 30 34 Jan 3 194

both of which exert unfavorable effects on thoracic injuries Strapping the chest reduces the effective excursion of the chest wall and thus reduces tidal air and vital capacity and lessens the effectiveness of the cough reflex Sedatives especially opiates depress respirations decrease pulmonary ventilation and diminish the sensitivity of the cough reflex smaller doses of these drugs do not control pain The only absolute contraindications are known hypersensitivity to procaine or epinephrine hydrochloride and/or sensitivity to the quinine series of drugs (eucupine) and a dirty or infected open wound in the skin that cannot be blocked from the field of injection

[Early reli f of pain an] tead in of the chest help to prevent compl cating pneumon a whi h ometimes develop when trauma of the chest wall i exten ve —Ed]

Tuberculosis of the Sternum is rare according to Joseph D Wassersug[3] Of 1 134 cases of bone and joint tuberculosis seen at the Lakeville State Sanatorium Middleboro Mass from 1926 to 1940 the diagnosis of tuberculosis of the sternum was made in only 12 Seven of the patients were females and five males The a es at onset varied from 1½ to 70 there was no preponderance of any age group In no case was there a history of trauma Eleven patients had other tuberculous lesions A painless swelling in the region of the sternum was a presenting symptom in seven cases pain was in early symptom in only three and a discharging sinus was the chief complaint in two Eventually one or more draining sinuses develops in practically every case It is often difficult to make a correct diagnosis before a sinus develops Material that drains or is obtained at operation should be subjected to thorough pathologic study including guinea pig inoculation In eight cases such material confirmed the diagnosis of tuberculosis in four the diagnosis was made on clinical and roentgenographic evidence alone

(3) N w E gl J Med 2 5 445 447 Sept 18 1941

Tuberculosis of the sternum must be differentiated from that of the chest wall ribs and costal cartilages and from tuberculosis of lymphatic vessels of the anterior costal interspaces or of the internal mammary or sternal lymph nodes, with abscess formation Tuberculosis of the breast must occasionally be considered Injection of radiopaque substance under such circumstances readily gives the clue to the actual process. Syphilis is differentiated by the Wassermann test and nontuberculous osteomyelitis of the sternum by the negative tuberculin test Biopsy rules out sarcoma cyst lipoma or fibroma

In 25 per cent of the cases the tuberculosis of the sternum became arrested spontaneously and the sinuses healed In the remaining 75 per cent operative procedures such as aspiration incision and drainage curettage and the resection of sinuses were performed The operative end results were usually good regardless of the procedure Two patients are still hospitalized and a third died while in the sanatorium Of the nine discharged two have died and one was lost from observation In no fatal case could tuberculosis of the sternum be regarded as a cause of death Six patients were followed from 10 months to 11 years with an average of over 6 years In only one patient does slight drainage still persist None of the others have had any recurrence of the disease

[Tuberculosis of the sternum seems most often to be due to lymphohematogenous infection and in these cases search should be made for other foci of disease —Ed]

Subphrenic Abscess with Bronchial Fistula Jerome Head and Theodore R Hudson[4] (Veterans Administration Hines Ill) point out that hepatic subdiaphragmatic and perinephritic abscesses frequently perforate the diaphragm and are evacuated by expectoration In a collected series of 890 cases Piquand found that this complication occurred in 12 6 per cent In a later

(4) Surg Gyne & Obst 5 54 60 July 1942

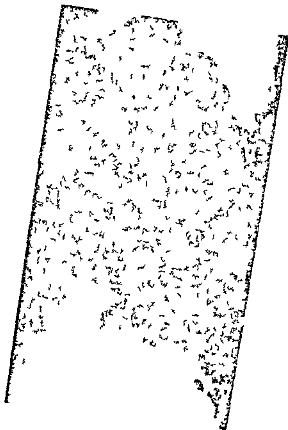
series of 3 608 cases Ochsner and DeBakey found that it occurred in 10 5 per cent The complication usually occurs late and is a result of delay in diagnosis or treatment It may develop as early as the tenth day of the disease

Perforation of a subdiaphragmatic abscess into a bronchus is usually sudden A patient who has pre

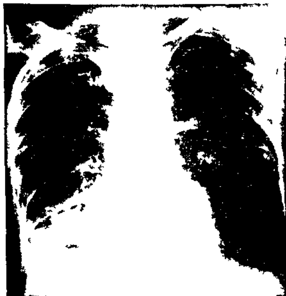


Fig 37 —Fi l right d ph gm w th m m l pulm ry fi d g uffi t t t f p xp t t gg t d d gn d g t p m p t eum p f m d A b th l ft d ph gm b t n b tl ght b t d f ubd ph gm t l

sented the picture produced by encapsulated pus suddenly starts coughing and in a few minutes expectorates a large quantity of pus Sudden death from drowning in pus may occur Flooding of the lungs with pus may produce progressive and fatal bronchopneumonia If the patient survives these immediate hazards he is usu



expectoration is one of the important diagnostic signs A comparison of x ray films taken before and after perforation gives important clues Films taken after injection of 300 to 400 cc air into the peritoneal cavity are of great value In the presence of subdiaphragmatic abscess no air can penetrate to this space on the af



F 39—S bd gh gm t b w th b h l fi t t th ft p h ll p f t n f pept l p t d ty w th fl i l l t ba f ght th tt d p b l flt t th gh t both
i g

fected side In acute unperf r it d subphrenic abscess exploratory aspiration is dangerous for leakage of pus into the punctured pleural spa e may cause empyema

In Steele s series of 48 cases of subphrenic abscess mortality was 50 8 per cent of his 6 patients with bronchial fistula died (mortality 50 per cent) In a personal series of 75 cases of subphrenic abscess re

ported by Ochsner and DeBakey, mortality in those with thoracic complication was 50 per cent as compared with 16 3 per cent in those without this complication. Treatment of subphrenic abscess with bronchial fistula is the same as that of uncomplicated subphrenic abscess namely incision and drainage

Three cases of chronic subdiaphragmatic abscess with bronchial fistula are reported in all of which recovery followed operation

[The pain of diaphragmatic hernia may simulate that of acute coronary insufficiency —Ed]

Parasternal Diaphragmatic Hernia with Report of a Case on the Right Side Rudolph A Colmers[5] (Columbia Univ) believes this to be the only reported case of right sided parasternal hernia with an acquired total atelectasis of the middle lobe of the right lung

The early history contained no incidence referable to parasternal hernia At the age of 41 the patient had appendectomy for right abdominal pain the appendix was normal Cholecystectomy performed a few months later for persistent pain revealed stones The operation was followed by continuing pain attributed to traumatic neuritis of the right arm At 62 she began to have bronchitis with marked dyspnea and cardiac insufficiency At this time the first x ray examination of the chest was made revealing a peculiar shadow in the right lung field The possibility of neoplasm was considered In the following terminal 15 years the x ray findings remained essentially the same From one of the early films, an encapsulated interlobar effusion was suggested and paracentesis advocated but not performed At no time was barium contrast medium given The patient developed hypertensive cardiovascular disease with high blood pressure She died at 77

Autopsy showed that the diaphragm was at the level of the fifth rib on either side Behind the lower border of the sternum at the level of the junction of the cartilage of the seventh rib with the sternum slightly to the right of the mid line, was an approximately round hole 5 cm in diameter on the under surface of the diaphragm Localization of the hole corresponded to the right space of Larrey This hole was the orifice of a hernial sac which extended upward, out

(5) Radiology 37 733 39 December 1941

ward and slightly posteriorly into the right thoracic cavity reaching the level of the third rib anteriorly. It consisted of firm connective tissue with no muscle fibers. The sac was entirely covered by serosa. Its anterior wall was formed by loose richly vascular connective tissue, the [illegible] and the posterior wall by the tendinous portion of the diaphragm. Its inner surface was lined by peritoneum. In the

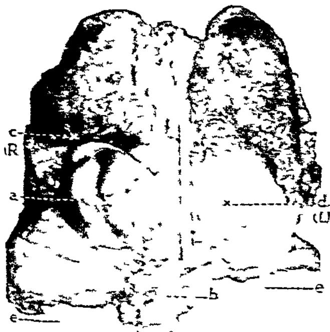


Fig. 41.—Hernia sac [illegible] with transverse [illegible]

hernia a loop of transverse colon, part of the great omentum, and the upper part of the round ligament of the liver were found. The contents were not adherent and were easily removed.

Most remarkable was the massive [illegible] lung which was reduced to a thin [illegible] I [illegible] a [illegible] no-[illegible] apparent [illegible] primary tuberculous

ported by Ochsner and DeBakey mortality in those with thoracic complication was 50 per cent as compared with 16 3 per cent in those without this complication Treatment of subphrenic abscess with bronchial fistula is the same as that of uncomplicated subphrenic abscess namely incision and drainage

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(5) Radiology 3 733 39 December 1941

from the smears of the lesser dosage diminished rapidly and was barely demonstrable at four hours in case of sputum and at one day in the case of the water preparation

In the second experiment the viability of dried tubercle bacilli was studied in roomlight and in complete darkness The dosage of bacilli per smear was 0 005 mg The test was run in the early spring during cloudy and even rainy weather Bacilli were recoverable by culture at one day i e after exposure to 12 hours of light but not at two days In the dark they were recoverable at 9 days but not at 40 There was no demonstrable difference between viability in sputum and water preparations

A third set of tests was run in midsummer To improve chances of recovery the dose per smear was 0 5 mg The preparations were exposed to both roomlight and dark Guinea pig inoculations and cultures were used for recovery Living tubercle bacilli were demonstrable after 51½ hours in roomlight and 55 days in the dark In roomlight cultures were negative at 56½ hours and the animal inoculation was negative at 4 days In the dark culture was negative at 75 days but no further animal inoculation was made Tubercle bacilli lived longer in sputum than in water smears

The following winter sputum smears containing 0 5 mg bacilli were exposed in roomlight dark and in the electric refrigerator The bacilli survived about 5 days in roomlight from 3½ to 5 months in the dark and from 6½ to 14 months in the refrigerator

Results of the experiments indicate that tubercle bacilli live a short time in rooms well supplied with unfiltered daylight they are more readily recoverable when the dose deposited is greater they live longer in smears made from sputum than from water suspensions they live longer in winter than in spring and summer Variations in relative humidity and periods of partial cloudiness have no demonstrable effect on

teen Its bronchus wa ot normal caliber but 1 cm from its root it showed an upward kink and from this point on the lumen was collapsed Micro copic examination revealed ad van d atelectasis and fibrosis with much coal pigment pre ent Corpora amylacea were found in some of the alveolar paces Elastic fibers were abundant and were also present in the collapsed alveolar walls The right lower lobe was lightly impre ed by the hernia but not atelectatic The markedly enlarged heart (cor bovinum) was displaced to the left

This parasternal diaphragmatic hernia probably developed during adult life because (1) the patient's a e and obesity would predispose to parasternal hernia (2) the clinical symptoms referable to the hernia did not manifest themselves until the patient was middle aged (3) the many elastic fibers in the alveolar walls of the atelectatic portion of the lung prove that this compression atelectasis developed in extra uterine life (4) the abundant coal pigment in the atelectatic lobe shows that this condition must have been acquired late in life

TUBERCULOSIS

Bacteriology Practical Technics

Survival of Tubercle Bacilli was studied by C Richard Smith[6] (Los Angeles) Suspensions of virulent human tubercle bacilli in water or sputum were used In the first experiment smears containing 0 0000 and 0 0 mg tubercle bacilli respectively were exposed to unfiltered north room daylight during a clear dry period in midwinter The micro organisms survived a maximum of four days i e exposure to 40 hours of daylight Recovery was by culture There was heavy growth from both smears containing the greater dosage (0 0 mg) at one day while at four days only the sputum smear was positive and then to a minimal degree All cultures were negative at 12 days Growth

(6) Am R v T 1 4 334 34 M r 1 194

A comparative study was made of 300 sputums examined coincidentally by the Clorox and the sodium hydroxide methods 200 by the chemical flocculation method 100 by the papain method and 500 with direct smears of choice particles The results revealed that there was no positive finding by any other method which was not confirmed by the Clorox method while conclusive evidence was shown of the superiority of Clorox as a digestant Furthermore instances were noted in which the Clorox method actually demonstrated an increase in tubercle bacilli over 300 times that of their showing in direct smears of the same positive specimen In specimens repeatedly negative by the direct smear method as high as 50 tubercle bacilli were persistently found by the Clorox method Clorox has been found equally efficient in the concentration of tubercle bacilli in other body fluids

[This method is also described in the *American Review of Tuberculosis* for April 194_ —Ed.]

Value of Fluorescence Microscopy for Demonstration of Tubercle Bacilli in Sputum The question whether fluorescence microscopy constitutes an actual progress as compared with the older methods was investigated by P N Oscarsson[8] (Univ of Lund) Sputum was examined by the fluorescence Ziehl Neelsen culture and guinea pig methods In most instances in which the direct smear examination was negative the stomach contents were sent in addition to the sputum for culture and guinea pig inoculation Two counterstaining technics were used in the Ziehl Neelsen procedure (1) the usual borax methylene blue technic (blue smear) and (2) the 1 per cent picric acid technic (yellow smear) The latter was easier to handle and more efficient for finding of bacilli which stand out as bright red elements against the pale yellow background whereas the blue stain occasionally covers the bacilli especially in thick and unevenly spread smears For fluorescence

(8) A t m d S dn 104 40 50 1941

viability of the bacilli Probably unfiltered daytime roomlight can play an important role in preventing cross infections and in protecting the employes of tuberculosis sanatoriums and rest homes

[Jacobs and Petroff (*Quarterly Bulletin of Sea View Hospital* October 1941) found it difficult or impossible to isolate tubercle bacilli from books and garments of tuberculous patients who had coughed freely toward these articles They consider that storage of books for several weeks and exposure of garments to the sun and air for a few days are probably sufficient to kill the contaminating tubercle bacilli —Ed]

A Rapid Method for Concentration of Tubercle Bacilli is described by Edward L Halliman and Theodore R Reusser[7] (Veterans Administration, Tucson Ariz) The digestant used is Clorox, a solution manufactured for use as a bleacher deodorizer and disinfectant Its active ingredient is 5 25 per cent sodium hypochlorite Caustic soda, lime acid and harsh substances have been removed The Clorox method has the following advantages It is by far more rapid than any technics now used digestion being completed in two minutes Clorox is economical and produces no bulky sediment the latter consists mainly of tubercle bacilli The sediment needs no neutralization and no fixing on the slide Tubercle bacilli are killed durin the digesting and centrifuging processes thus makin the material safe for handling by the laboratorian.

METHOD —From 5 to 10 cc sputum is placed in a flask or wide mouthed bottle with twice the volume of commercial Clorox and after being shaken several times over a 2 minute period the mixture is set aside at room temperature for 10 minutes It is then poured into a conical tube and centrifuged at 3 000 revolutions for 10 minutes A fine creamy white sediment forms in the bottom of the tube The supernatant liquid is poured off and with an applicator a small drop of the sediment is transferred to a slide the slide dries at once and is stained by the usual method No long shaking and incubation periods are necessary The method is a slightly modified method of Oliver and Reusser in that equal volumes of Clorox and sputum were used in the original procedure

(7) M B U V t Adm n 18 03 0 Oct 1 1941

the blue and yellow methods was shown in the greater number of positive findings Because of the hazard of overdiagnosis a certain critical attitude is indicated especially in cases with scanty bacillary findings The cultural and the guinea pig procedures are superior to fluorescence microscopy

[This work should be compared with that described in the following article In view of the present difficulty of securing new laboratory apparatus it would be desirable to have a further trial of the dark field method of Osol Another new staining method is described by Weiss (*American Review of Tuberculosis* 46 199 04 August 1942) He claims the advantage that with his new stain tubercle bacilli and other bacteria appear larger and thicker and contrasting stains are quite vivid —Ed]

Dark Field Demonstration of Tubercle Bacilli in Direct Smears Stained According to Osol As the Method of Choice is described by Heinrich Egli[9] (Zurich) A comparative study was made on 310 positive sputums laryngeal smears pleural exudates urine sediments and pus smears Examination was made of the same *specimen by the Ziehl Neelsen light and dark* field method and by the Osol dark field method In regard to the relative content of bacilli after Gaffky and the time necessary for detection of the first bacillus the Osol method proved six times superior to the Ziehl Neelsen method In addition 15 sputums which were repeatedly Gaffky 1 positive by the Osol method but negative with the Ziehl Neelsen light and dark field method were found positive on culture

OSOL TECHNIC —The proper carrying out of this technic is important for the dark field examination The smear must be as thin as possible to obtain good contrast Moreover thick slides contain too much light dispersing material After fixation the smear should dry in air for several hours To prepare for this examination cover the slide with carbol fuchsin and bring to a boil three times Decolorize with 5 per cent sulfuric acid and wash with water Rinse with 10 per cent sodium sulfite solution or better still with ammonia for 10 to 15 seconds then wash with water

(9) S hw m d W h h 166 169 F b 7 194

microscopy the previously described staining method was used with a slight modification

A comparison of the smears stained for fluorescence with those stained by the yellow or blue technic revealed bacilli in one two or all three smears in 142 of the 600 sputums examined Of these fluorescence microscopy gave positive results in 131 failing in the other 31 in which the yellow and or blue smear was positive Of the 131 sputums only 100 were positive in the yellow and or blue smears Study of the time factor involved in finding the bacilli revealed that if the sputum is positive 6 seconds are required with fluorescence microscopy 20 seconds for the yellow smear and 45 seconds for the blue smear In instances in which the findings were positive on fluorescence microscopy only the time required for finding bacilli by this method was 28 seconds

A comparison of the results obtained by the fluorescence technic with those obtained by the cultural and guinea pig technics was made in 131 cases In 28 the direct staining methods including the fluorescence technic gave positive results and as was to be expected the culture and the guinea pig tests were likewise positive In 70 cases the findings were negative on fluorescence microscopy and on culture and guinea pig procedures In 25 cases fluorescence microscopy showed tubercle bacilli whereas the results were positive culture and guinea pig inoculation In four cases the fluorescence findings were positive while cultures and guinea pig tests of both sputum and stomach contents were negative In four cases all three methods showed bacilli whereas the blue and yellow smears were negative

This investigation indicates that the greatest value of fluorescence microscopy lies in the rapidity with which bacilli can be detected in a positive sputum in which respect the method is far superior to the Ziehl-Neelsen carbolfuchsin stain Its further advantage o

seen with the 1/12 in objective in 24 hours Colonies may be just perceptible with the in objective in 48 hours In a week the cultures are well grown Besides killing nonacid fast organisms the acid exerts a coagulating effect on mucus This is an advantage as the process is one of fixation Most of the cellular elements of the sputum film autolyse (Figs 41 44) Two technics are described one of which is presented here

F g 41 1 2 —) r t m film n
F g 4 (ght)—( ) f m p t ft th d y b t

TECHNIC—The sputum is spread and dried on a 4 in Petri dish with a flat or slightly hollow bottom surface The film is treated with 15 *per cent sulfuric acid for five minutes* The acid is removed with a large teat and pipet and the film is flooded with 5 *cc sterile distilled water* This is allowed to act for a minute and the washing repeated The medium (5 cc citrated blood and 5 cc water or 1 *per cent saponin*) is then added and the dish placed in the incubator for a week The medium is then washed off with water and the film stained

As in Ziehl Neelsen's stain the principle of this stain is the acid fastness of the tubercle bacilli. It differs from the former by the repeated decolorization with sodium sulfite or ammonia and in that no counterstain is used. This results in better contrast presentation. Since the light dispersing elements are distributed in an optically empty medium only the glowing yellow green rods of tubercle bacilli are visible against a black background. As in the dark field, the bacilli are self illuminating; they appear large to the eye and a 400- to 500 fold magnification is sufficient as compared with the 800 to 1 000 fold magnification with ordinary illumination. An added feature is that by simple manipulation of the diaphragm the dark field may be changed into a light field and the rods identified by their red color. Unlike the plain Ziehl Neelsen method the Osol dark field method renders also the less acid fast tubercle bacilli visible. The differentiation of tubercle bacilli from acid fast bacilli occurring in purulent bronchopneumonia, in lung abscess and in bronchiectasis is not possible in the dark field except perhaps with the presence of Much's granules.

According to Pothmann the fluorescence method is not superior but equivalent to Osol's method which is 10 times less expensive and much easier to handle.

Sputum Film Cultures of Tubercle Bacilli. Method for Early Observation of Growth is described by D M Pryce[1]. The principle of the method is that sputum films dried on glass may be treated with acid to destroy other organisms than tubercle bacilli and incubated in contact with hemolysed blood, the tubercle bacilli being thereby transformed into micro colonies which can be stained with Ziehl Neelsen and studied with the low power microscope. The technic may be carried out on the floor of Petri dishes in vaselined rings on micro scope slides etc. The method is also applicable to pus and caseous material. Obvious signs of growth can be

(1) J P th & Bact 53 327 334 November 1941

Pennsylvania) An endeavor was made to determine whether phagocytic mononuclears of immunized animals removed from the influence of the organs in which they are naturally situated will inhibit the growth of tubercle bacilli in their cytoplasm more effectively than similar cells obtained from normal animals. It was also undertaken to ascertain to what extent the inhibition of growth of tubercle bacilli in the immunized animal is due to cells themselves and to what degree it is accounted for by the immune body fluids which bathe them.

The anterior chambers of normal albino rabbits were used as in vivo incubators. One anterior chamber was host to one type of cell or cell serum mixture while the other anterior chamber of the same rabbit was host to a cell type or cell serum mixture to which the first was to be compared. The fate of the bacilli in each cell type and in each fluid menstruum was culturally determined by comparing the number of living bacilli present in the cells originally implanted with the number of living bacilli that were contained in these cells after they have grown in the chambers. The implanted cells were identified by carbon particles ingested by these cells at the time that the bacilli were phagocyted.

Cells of immunized animals which have phagocyted tubercle bacilli in vivo in lymph nodes or bone marrow and had been transferred two days later into the environment of the chamber fluid of a normal rabbit inhibited the growth of the micro-organisms within their living cytoplasm for two weeks in the absence of immune body fluids. Similarly transferred normal cells under these conditions permitted the bacilli to grow within them to a much greater extent. To what degree the inhibition of growth in these "immune" cells was due to the immune body fluids which had formed a film about the bacteria before their phagocytosis or to the mere sojourn of the bacilli in these phagocytes in the body of the immune animal for two days before their trans-

with Ziehl Neelsen Counterstaining with methylene blue can be omitted The culture is examined under low power

The method is especially suitable for study of early growth as the colonies are examined in situ with little or no disarrangement of their structure With succes-



Fig 43 (left) — C l n f ... Fig 44 (right) — C ... ding after ... d y ... in ubation × 00

ful incubation the chances of finding tubercle bacilli in a film are increased about 100 times

PATHOLOGY AND IMMUNITY

Studies on the Mechanism of Immunity in Tuberculosis Fate of Tubercle Bacilli Ingested by Mononuclear Phagocytes Derived from Normal and Immunized Animals was studied by Max B Lurie (Univ of

(2) J Exper Med 75 47 68 Mar 1 194

inhibition of multiplication of tubercle bacilli in the re infected animals rests chiefly on the increased capacity of the mononuclear phagocytes of the immunized animal to destroy or inhibit the growth of the bacilli which is independent of immune body fluids or of the organ environment *in which they grow*

Cellular Reactions to Fractions from Tubercle Bacilli Florence R Sabin[3] (Rockefeller Inst) states that in general every cellular reaction recognized in the lesions of tuberculosis can be reproduced by fractions isolated from tubercle bacilli but that none of the fractions thus far studied has brought about any change in re sistance to the disease The materials studied were lipids waxes polysaccharides and proteins The tuber culolipids and proteins all induced a new formation of monocytes The phosphatide changed monocytes into epithelial cells and their derivative giant cells the waxes induced the fusion of monocytes into foreign body giant cells the proteins induced a more varied stimulation of monocytes i e into epithelioid cells macrophages and both types of giant cells *These reac tions were least with the soluble form and most with the insoluble and in every instance they were intensified in tuberculous animals The polysaccharides were chemotactic to neutrophilic leukocytes monocytes were involved only indirectly in that they eventually phago* cytized extravasated neutrophilic leukocytes

Sensitization to tuberculoprotein as expressed by the delayed tuberculin type of skin reaction was produced by tuberculoproteins derived from synthetic protein free mediums on which tubercle bacilli had been grown and from bacilli themselves The power of the tuberculo protein to induce skin sensitization was markedly en hanced by the addition of tuberculophosphatide to the protein The action of the phosphatide was to induce tubercle formation The sensitization induced by pro tein differs from the conditions of sensitization or al

(3) Am R Tuberc 44 415 4 3 Oct 1941

plantation to a normal environment could not be determined by these experiments To answer the latter question exudative mononuclears derived from normal and immunized animals washed free of their body fluids were permitted to ingest tubercle bacilli and carbon particles in vitro in the serum of the normal or of the immunized donor of cells Before incubating the phagocytes in the anterior chambers the supernatant fluid of each phagocytic mixture was replaced by the same fresh serum in which the phagocytosis had taken place Under these conditions it was found that immune cells that had ingested tubercle bacilli in vitro in the presence of immune serum inhibited the growth of tubercle bacilli in their cytoplasm to a much greater extent than normal cells that had phagocyted the bacteria in the same medium Furthermore, the absence of immune serum in the medium of phagocytosis and growth of cells obtained from immunized animals did not rob them of their greater bacteriostatic properties on the growth of tubercle bacilli within them nor did the presence of immune serum during phagocytosis impart to cells of normal origin a significant and constant bacteriostatic effect

Immune phagocytic cells possess in themselves apart from the immune body fluids a greater bacteriostatic property on the growth of tubercle bacilli within them than do normal cells This demonstration of the inherent bacteriostatic property of the immune cells is in harmony with the previously demonstrated increased capacity for phagocytosis of tubercle bacilli possessed by cells of actively tuberculous rabbits which is also independent of the medium in which the phagocytosis occurs This enhancement of phagocytosis parallels the immunity of the possessor of such cells Treatment of rabbits with tubercle bacilli of low virulence confers little immunity to the infection and little or no enhancement of the inherent phagocytic capacity of their cells for tubercle bacilli Thus the destruction or

essentially the same in examination of tissues as of smears An additional problem is encountered however because of the difficulty of decolorizing the tissues after staining with the fluorescence dye and because the natural fluorescence of some tissues is sufficient to interfere with the contrast between the stained organism and the tissue background This interference was found to be particularly troublesome in tissues from the central nervous system With the use of the simplified fluorescence equipment described by Richards and Miller and the auramine staining and decolorizing solutions as modified by Thompson the following technic has been satisfactory for demonstrating Mycobacterium tuberculosis in tissues

TECHNIC —Tissue blocks fixed in formalin and embedded in paraffin are sectioned at 5 μ and mounted on glass slides with a minimal amount of egg albumin When the sections are dry the paraffin is removed in the usual manner and the deparaffinized sections covered with the auramine staining solution for five minutes The sections are washed and covered with the decolorizing solution (alcohol 70 per cent 100 cc concentrated hydrochloric acid 1 cc and sodium chloride 0 5 Gm) for 20 minutes The sections are then washed with tap water and covered with fresh decolorizer for another 20 minutes The tissue is washed with tap water and counterstained with an aqueous solution of methylene blue (0 1 per cent) for one minute then washed dried and examined with the fluorescence microscope without using a coverglass The methylene blue gives a black or dark blue background but does not interfere with the fluorescence of the micro organism the bacilli stand out as bright yellow rods The organism can be identified readily by using an 8 mm objective and a × 25 ocular

A comparison of the auramine method with the usual Ziehl Neelsen method was made by cutting two sections from each of 130 blocks of tissue and staining one section from each block with auramine and one with carbolfuchsin Material was selected from tissues obtained at autopsy which were histologically tuberculous and from granulomatous lesions of doubtful causation Results showed that an ordinary sized tissue section could

and respiratory rate Laboratory tests include red and white blood cell counts differential counts hemoglobin assays sedimentation rate and sputum or gastric content procurement for smear culture and animal inoculations

Scope of Program —The case finding should include every student and teacher In addition all employes who handle food water ice or linen or work in close contact with students should be examined The individual with an open or progressive lesion should preferably be referred to a good sanatorium The exceptional individual who may be left on the campus (perhaps with pneumothorax) should room alone be excused from physical education barred from competitive athletics and kept under constant scrutiny

TUBERCULIN TESTING OF AMERICAN COLLEGE STUDENTS 1932 TO 1941

YEAR	TOTAL TESTED	POSITIVE %	MEN POSITIVE %	WOMEN POSITIVE %
193 33	14 318	35 0	35 0	27 0
1933-34	25 184	30 3	[illegible]0 0	26 0
1934-35	26 861	29 4	30 0	27 8
1935-36	31 601	30 0	31 0	28 0
1936-37	5[illegible] [illegible]24	27 3	[illegible]9 4	24 8
1937-38	64 232	25 8	29 8	23 5
1938-39	8[illegible] [illegible]74	25 5	27 0	21 3
1939-40	1[illegible]3 389	25 4	[illegible]6 5	22 0
1940-41	149 744†	20 7	22 8	18 5

l th t m ll g f l t d ff t t th t by es f th m f thos th t th t tal n mb test d is u lly l ghtly port d cc d g t q est o bly d qu t m y rvey po t d
† Dosag

Primary Tuberculosis in Adolescents and Adults

G Gregory Kayne concludes from published reports that at least half the people in civilized communities first become infected with tuberculosis after adolescence The rate at which infection occurs from then on appears to depend on opportunities for contact with the disease Published investigations suggest that most of the late

(7) P P y So M d 35 493 494 May 194

while all chests that contain tuberculous lesions not demonstrable on standard postero anterior views and any that harbor lesions too minute to be recognized macroscopically will be passed by the roentgenologist as normal or negative The intradermal technic of Mantoux is recommended as the most accurate and safest method The minimum procedure in college should include testing of all new students and employes and annual retesting of all previously negative reactors In groups where hazards of exposure are extraordinarily high as amon medical and nursing students tests should be repeated every three months or at least semi annually Purified protein derivative is recommended as somewhat more specific and less liable to false reactions but any reliable brand of old tuberculin will give excellent results if freshly mixed and properly used In large scale testing the tuberculin should be checked by giving a test dose to a known positive reactor A two dose Mantoux test is essential a primary minute dose to avoid harm to the hypersensitive individual and the greatly multiplied second dose to identify those truly positive tuberculin reactors with a low degree of skin allergy Standard tuberculin syringes and platinum iridium needles of the Schick test type that may be flamed handily between tests should be used

Roentgenograms of the Lungs—Roentgen examination of all positive reactors should be made at once, it should be repeated at least annually or oftener when findings suggest its need Full sized single celluloid films or fine quality paper films now supplied by manufacturers are the best filming mediums Mobile x ray units are an expedient and accurate means of filming students in campuses where x ray facilities are lacking Fluoroscopy (possibly including spot films of Stiehm) should be widely used but always as an adjunct to the best available filming methods

Clinical and Laboratory Tests—Students with suspected lesions should be observed for temperature puls

and respiratory rate Laboratory tests include red and white blood cell counts differential counts hemoglobin assays sedimentation rate and sputum or gastric content procurement for smear culture and animal inoculations

Scope of Program—The case finding should include every student and teacher In addition all employes who handle food water ice or linen or work in close contact with students should be examined The individual with an open or progressive lesion should preferably be referred to a good sanatorium The exceptional individual who may be left on the campus (perhaps with pneumothorax) should room alone be excused from physical education barred from competitive athletics and kept under constant scrutiny

TUBERCULIN TESTING OF AMERICAN COLLEGE STUDENTS 1932 TO 1941

YEAR	TOTAL NO TESTED	POSITIVE %	MEN POSITIVE %	WOMEN POSITIVE %
193? 33	14 318	35 0	35 0	27 0
1933–34	?5 184	30 3	30 0	26 0
1934–35	26 861	?9 4	30 0	27 8
1935–?6	31 601	30 0	31 0	28 0
1936–37	56 2?4	?7 3	29 4	24 8
1937–38	64 ?32	25 8	29 8	23 5
1938–39	8? ?14	2? 5	?? 0	24 3
1939–40	1?3 38?	2? 4	26 5	2? 0
1940–41	149 744†	20 7	?? 8	18 5

In th t m ll g f l t d ff t t th t by th t th t t ? mb t ted lly l ghtly f ch m l thos po i d d g t

† Dos g is q t n bly d q t m y y po t d

Primary Tuberculosis in Adolescents and Adults[7] G Gregory Kayne concludes from published reports that at least half the people in civilized communities first become infected with tuberculosis after adolescence The rate at which infection occurs from then on appears to depend on opportunities for contact with the disease Published investigations suggest that most of the late

(7) P c R y S c M d 35 483 494 M y 194

primary infections occur between 16 and 30 While among the general population the increase in incidence of infection is more or less gradual, among certain groups exposed to special risks such as medical students and nurses the increase may be rapid

The primary lesions in adolescents and adults are similar to those in children However, unlike in children caseation in the corresponding hilar glands may be less extensive than in the pulmonary focus and presumably because of this, epituberculous lesions, so common in childhood and caused either by collapse or by perifocal inflammation are rarely observed The evolution of the disease differs little from that seen in childhood from its most favorable outcome—calcification of the primary complex—to the unfavorable disseminations both acute and chronic There is one difference In adolescents and adults in a comparatively short time of the apparent healing of the primary complex, whether insignificant or extensive lesions typical of bronchiogenic tuberculosis may develop This has been demonstrated in all relevant morbid anatomic material available This fact cannot be overstressed since it is evident that when the primary lesions are insignificant and not demonstrated clinically the onset of lesions of the bronchiogenic type within some months of the change in tuberculin reaction might be regarded by the clinician as a form of the primary lesion itself

The clinical manifestations and symptoms of primary tuberculosis in adolescents and adults are discussed on the basis of findings of Malmros and Hedvall and Kaynes own series Among the 151 patients of Malmros and Hedvall who became tuberculin positive during observation only 47 showed clinical manifestations Those with erythema nodosum with or without primary complex had fever cough and pain in the side and the sedimentation rate was nearly always increased When a primary complex alone was seen there were generally fever cough fatigue pain in the chest catar

rhal symptoms and increased sedimentation rate Onset of the subprimary initial foci was usually associated with no symptoms and a normal sedimentation rate When symptoms did occur they were flu cough fatigue fever and hemoptysis In most of the students and nurses the lesions were detected only by systematic roentgen study Similar findings were recorded in Kayne s series of 20 cases

Discussions on endogenous and exogenous reinfections are largely academic When there are many uninfected adolescents and when bronchiogenic tuberculosis may follow soon after the primary infection exogenous infection as a cause of bronchiogenic tuberculosis plays an essential role Thus both contact and lowered resistance are important in control of the disease Continuous stress should therefore be placed on the importance of reducing the human tubercle bacilli reservoir not only in homes but in crowded communities by detection of symptomless disease through mass roentgenography by adequate and immediate facilities for treatment and by provision for institutionalization of persons with bad and good chronic cases

W Pagel states that an inactive primary complex is found in a large proportion of healthy individuals under 18 Recently however incidence of tuberculous infection in the general population has undergone a remarkable change only 20 per cent (as against 60 per cent before) show evidence of primary infection up to the age of 18 while figures up to 100 per cent are only reached in the highest age groups It is therefore to be expected that a larger proportion of adults than before should show evidence of fresh primary infection

Autopsy observations by Pagel in 13 cases of primary tuberculosis of adults had one feature in common in the lungs or in the intestinal tract there was a caseous (or ulcerative) focus with similar changes in the corresponding lymph nodes a fresh primary complex In all cases this was clearly differentiated from other

tuberculous lesions Careful dissection and screenin of the lungs showed that no traces of infection older than this primary complex were present True reinfec tion i e establishment of a lesion with all anatomic characters of the primary complex in a case in which the calcified or ossified residues of a previous primary infection were found has been recorded but is not fre quent enough to discredit the current anatomic view of primary infection i e that this occurs only once in life as a rule In Pagel s present series no calcification was seen and thus the fact was established that a recent primary infection in adult life was present Ages ranged from 15 to 40 Of the 13 cases 3 were intestinal and 10 pulmonary infections The changes in most cases resembled those seen in childhood The primary focus was found in the lower parts of the lungs usually near the base and not far from the pleura In one respect a difference was found In children the primary focus as a rule is smaller than the changes in the lymph glands In the present series of adults this ratio was reversed in four of eight cases of pulmonary infection and in one instance primary and glandular foci were about equal in size and very small Despite the com paratively small size of the glandular changes the classic picture of the primary complex does appear in adults just as in children A fresh tuberculous primary complex occurs in adults associated with postprimary (disseminated and bronchiogenic) as well as without postprimary tuberculosis Tuberculosis obeys the laws of primary infection irrespective of age and natural resistance

Causes Underlying the Recent Increased Incidence of and Mortality from Tuberculosis in Glasgow are dis cussed by Stuart Laidlaw and Duncan MacFarlane[8] (Pub Health Dept) For five years preceding the out break of war in 1939 the incidence of and mortality from pulmonary tuberculosis were tending to stabilize

(8) Brit M J 2 436 437 Sept 27 1941

themselves in Glasgow at figures around 1 600 notifications and 960 deaths per year During the first year of war there was a rise of approximately 250 notifications and 200 deaths during the first half of 1941 there were 1 095 notifications and 671 deaths indicating that the disease is continuing to increase in incidence The rise showed no seasonal preference The increased incidence occurred almost entirely between 15 and 45 in males and 15 and 35 in females both sexes showed an all around increase of 20 per cent over the 1939 returns

The comparative figures for nonpulmonary tuberculosis for 1939 and 1940 were 561 notifications and 255 deaths for 1939 and 669 notifications and 329 deaths for 1940 or an increase of approximately 17 per cent The spine meninges and lymph nodes showed the greatest increase while other sites remained relatively unaffected The increase occurred mainly in children of both sexes under 5 and to a lesser extent in females aged 15 25

Investigation of factors which might not have been present in 1939 or if present were intensified in 1940 led to the conclusion that it is a combination of long hours overtime strain and ill spent leisure which produces the rise in the number of cases of tuberculosis and that the increase will be maintained at least as long as these factors remain unchanged

[Recent reports indicate a rise in deaths from tuberculosis in France and Germany probably greater than in England. In the United States the death rate still continues to decline and the rate was reported to be 44 per 100 000 in 1941 —Ed]

Weather and Resistance in Pulmonary Tuberculosis W F Petersen J S Howe and M E Milliken[9] (Univ of Illinois) note that of all the clinical phenomena observed in the progression of tuberculous disease in the human the recognition of seasonal activation of the disease (evident in the usual clinical findings in complications and finally in death) is the most ancient and uni

(9) Am R T b 44 37 414 O t b 548 58 N mbe 1941

versally accepted For the patient who has established a modus vivendi it is the late winter and spring that is often associated with renewed signs of activation (tuberculin reaction loss of weight, increase of fever leukocyte count and sputum output etc) By season is meant merely the sum total of continued weather effects In considering weather effectors as they concern man they are thought of largely in terms of the energy requirement for adjustment Here the frequency of change the relative degree of change and the extremes involved are all of significance Particularly the passage of interfaces of the diametrically opposed air masses (warm tropical and cold polar air masses) representing contact zones of great instability, requiring rapid adjustment on the part of the human organism causes periods of great strain

The passage of a cold air mass over a region is associated with a relative sympathicotonia in the population and this is followed by a relative vagotonia, to use chemical equivalents it is associated with a relative alkalosis followed by a relative acidosis In terms of blood pressure a period of vascular spasm and increased systolic and diastolic blood pressures is followed by a reversal to lower systolic and diastolic blood pressures there is first contraction of the peripheral vascular bed (the organism tends to shut itself off from the environment) and this is followed by a relative peripheral dilatation In the first stage the capillary bed is less permeable in the second more permeable In the first stage there is relative lymphatic overbalance in the second, a myeloid overbalance

This meteorologically induced biologic pendulation of all physiochemical and physiologic overbalances must affect tuberculous foci The younger and more labile the focus and the more poorly encapsulated the greater will be the reactivity to weather (and seasonal) change the older and more stable the lesion and the more encapsulated the less will be the effect of these physiologic

and pathophysiologic alterations The effect of biologic pendulation will in general be as follows With the first phase resistance to tuberculous dissemination and progression will be increased i e with lessened permeability lowered metabolism increased alkalinity and relative lymphocytosis as well as dehydration the tendency to bacillary dissemination will be decreased tissue digestion and breakdown reduced intoxication lessened and clinical improvement become evident With the second stage the picture is reversed With every energy impact (limited here to the consideration of weather effects but all extraneous changes affecting the body must be considered) initiating such biologic pendulation the clinical outcome will depend on the net result i e on the attainment of a biologic milieu of greater anabolic potential (beneficial) or greater catabolic potential (harmful) Here obviously the available reserves (food stuffs vitamins buffers endocrines etc and the local cellular situation) will provide the background and condition the ultimate result

Six advanced cases of tuberculosis have been studied over long periods and the biochemical and clinical tide was investigated in relation to the meteorologic environment of the time The tests included blood pH carbon dioxide cholesterol the cell count quantitative tuberculin reaction and oxidative potential of the skin blood pressure sputum volume blood cultures with daily inoculation of guinea pigs etc In addition observations were made on the effect of continued alkalization The detailed protocols of the first patient are presented

From these observations and those previously published the authors draw the following conclusions

1 The trend to activation of tuberculosis observed in the late winter and spring is associated with the general tendency to increased catabolism evident in normal individuals as well as patients studied The lowering of the blood pH (relative acidity) and of the blood pressure (vascular and general cellular fatigue) along with

the increase in capillary permeability gives objective evidence that resistance to tuberculous extension decreases with organic (tissue) fatigue This organic fatigue results from the loss of buffers vitamins and essential mineral and organic constituents incidental to the repetition of environmental impacts of the severe meteorologic turbulence of the late winter and spring Basically it must be considered from the point of view of an energy deficit

2 An objective increase in resistance occurs with release from the meteorologic strain in the summer and autumn with increase in blood pressure increasing pH lessening of permeability of the capillaries etc

3 Every meteorologic change particularly the passage of clearly defined cyclonic fronts finds reflection in a changed biochemical status of the normal as well as the tuberculous individual Since this reaction is diphasic it may result in either harm or benefit to the individual who is ill depending on many adventitious factors such as the preceding state of the patient the availability of reserve the condition of the individual foci and the hormone balance (particularly the sex cycle)

4 It was demonstrated that an identical environmental situation that is reflected in the death of one patient may be associated with a beneficial change in the organic phase in a second patient

5 Experimental alkalinization apparently results in some increase in resistance to tuberculous infection

[This is probably the most comprehensive and scientific study which has ever been made on the relation of weather to resistance in pulmonary tuberculosis —Ed]

The Geriatric Aspect of Pulmonary Tuberculosis is discussed by Joseph T Freeman and Charles A Heiken[1] (Philadelphia Gen l Hosp) The frequency of this disease in older persons has not been generally appreciated The actual incidence would indicate that this large group is a major obstructive factor in the national tu

(1) Am J M S 20 938 J 1 1941

berculosis program of segregation of open cases The elements common to the older age bracket may be summarized as the different reaction of the older body to the tubercle bacillus the longer period in which the infection may have been present economic considerations the welfare of the younger members of the society the general difficulties in controlling older patients and the lack of an efficient medical and social approach to this problem

In 3 000 routine postmortem examinations at the hospital it was found that pulmonary tuberculosis was present in 25 per cent of the patients The older age group 60 and over comprised one third of the total necropsy figure and in this fraction there was 28 per cent of the total incidence of pulmonary tuberculosis Included in this 25 per cent were 11 per cent of the fibroulcerative 8 per cent of the miliary and 65 per cent of the healed fibroid forms of pulmonary tuberculosis If the tuberculosis figures could be applied to the general older age population it would appear that in persons over 60 5 per cent have fibroulcerative 0 5 per cent miliary and 15 per cent fibroid pulmonary tuberculosis A comparison by race showed that the active form of the disease was as common in elderly white persons as in elderly Negroes that the miliary form was somewhat more common in elderly Negroes and that the fibroid form was much more common in elderly white persons

A study of 136 protocols of older persons in the tuberculosis division of the hospital showed a positive family history in 26 per cent The symptom complex is quite like that seen in younger persons but may be obscured by the changes of increasing age or be interpreted as due to senile debility Cough and expectoration were the most common complaints but hemorrhage fever and night sweats were not uncommon As a rule the symptoms of onset of the pulmonary condition were mild Fifty one per cent of patients showed

a temperature elevation of at least several days duration during hospitalization Many discrepancies can enter into the evaluation of fever in the elderly the few times in a 24 hour period when the temperature is recorded self observation and the fact that the readings were oral Acute temperature observation in older persons can be obtained best by rectal thermometry The roentgen report confirmed the clinical impression in the 128 cases in which such studies were made In 56 per cent the fibroid form was present one plate showed the miliary form and the remainder the fibroulcerative form Cavitation was reported in 60 per cent of these cases A positive sputum was demonstrated by the routine stained smear method in 69 per cent of the series Eleven per cent of the patients had diabetes all had positive sputum and cavitation was reported in 80 per cent. Death occurred in 52 per cent of the 136 patients but among the diabetics the mortality was 60 per cent Only 6 of the entire group (44 per cent) received any active treatment Phrenic operations were done on two and pneumothorax was attempted on four with completely successful results in one hydropneumothorax developed in only one

Control of tuberculosis in the aged should include earlier diagnosis with more stringent isolation and more active treatment Establishment of separate communities for old tuberculosis carriers close to large municipalities or on the grounds of the state sanatoriums would be an interesting and not too costly experiment for one of the large states to undertake After the initial outlay the cost and maintenance plus the possible general lessened incidence of the disease would be less than the support of these patients in the more expensive general hospital to say little of the benefits to the state of a falling tuberculosis rate These homes would be limited in general to the older tuberculous patients for whom there exists no procedure that will render them safe to the community

Diagnosis

Tuberculosis among Selective Service Men in New York State Robert F Plunkett (New York State Dept of Health) points out that despite the apparent shift of the peak of mortality toward the older age group tuberculosis is still second in importance as a cause of death among men aged 20 to 34 while the *highest incidence of morbidity from tuberculosis is still in the age group 15 29 In most cases in which tuberculosis is diagnosed at a late age it could have been diagnosed earlier had the patients been examined roentgenographically at or about the age of 30* A considerable number of young men of military age may therefore be expected to have pulmonary tuberculosis In some cases it may have been diagnosed previously and the men will be rejected But often the men may have more or less extensive pulmonary tuberculosis and yet present neither symptoms nor physical signs The lesions may be of the torpid slowly progressing type which may remain quiescent for years and then suddenly flare up and become active once the equilibrium between the virulence of the infection and the defensive response of the host has been disturbed Experience also indicates that the physical stress of military life would expose to definite risks of illness and future disability any man who shows evidence of the reinfection type of tuberculosis Once men with active or potentially active tuberculosis have been admitted to the Army a dangerous situation has been created The unusual living conditions prevailing in Army tents or barracks present excellent opportunities for development of new infections and nothing can prevent the patients carrying the disease to others

At the induction stations of Buffalo Syracuse and Albany each selectee is sent to the x ray department immediately after registration The following criteria are used in classifying the roentgen data for acceptance

( ) W M d 1 611 6 3 [illegible] 1941

or disqualification of the selectees (1) Chest normal No roentgenographic evidence of tuberculous infection is present (2) Chest normal (acceptable under MR 1 9) This includes roentgenograms which show changes indicative of residual childhood infection shown by the Ghon tubercle or by slight calcium deposits in the mediastinal region with no enlargement of glands or those which show a slight amount of linear fibrosis (3) Chest positive for tuberculosis (disqualifying under MR 1 9) This includes all thoracic roentgenograms which show evidence of the reinfection type of pulmonary tuberculosis and all those which show manifest primary tuberculosis either in the exudative stage or with evidence of enlarged glands, with or without calcium deposits (4) Thoracic pathologic conditions (roentgen evidence of cardiac, pulmonary or other thoracic pathology)

There were 14 923 men examined roentgenographically at the aforementioned stations from November 1940 to March 1941 Of these 127 men were disqualified for military service because of roentgen evidence of tuberculosis In addition 21 men were disqualified because of thoracic pathology other than tuberculosis

Plunkett concludes that it would be relatively inexpensive to keep all men with reinfection type tuberculosis out of the Army now by taking thoracic roentgenograms of all prospective recruits whereas it would cost many thousands of dollars to give treatment and later compensation not only in the cases now existing but also in the secondary cases resulting from spread of infection Experience with the different available mediums for thoracic roentgenograms has led to conclusion that the 4 × 5 in roentgen photographic film is the most economical and most practical film available for screening large groups of persons

[At present practically all candidates for enlistment and induction in the armed forces in this country are receiving x ray examination of the chest —L]

Fluoroscopy in Diagnosis of Pulmonary Tuberculosis Using the published data and figures of even ardent protagonists of fluoroscopy L Henry Garland[3] (San Francisco) finds that the relative accuracy of this method is much lower than might be gathered from the conclusions of these authors He believes that the proper role of fluoroscopy in diagnosis of pulmonary tuberculosis is that of an adjunct to radiographic examination which must be regarded as indispensable in individual cases Fluoroscopy is of value in determining the aerability of various portions of the lungs especially those areas partly concealed by adjacent structures the mobility of the diaphragms and mediastinum and the behavior of apparently encapsulated collections of fluid or air It should be used in conjunction with properly made roentgenograms stereoscopic postero anterior films as well as lateral oblique or other projections as indicated in the individual case With fluoroscopic examination alone small tuberculous infiltrates especially in the apex and small active lesions elsewhere in the lungs are easily overlooked Existence of a significant tuberculous lesion cannot always be excluded by fluoroscopic examination especially in thick chested or fat individuals The observer tends to attribute undue significance to normal bronchovascular markings and normal variations in cardiovascular shape and size Bearing in mind these points and the importance of adequate adaptation fluoroscopy can be of considerable service in mass examinations being by far superior to routine physical examination for the discovery of pulmonary disease

The percentage error with fluoroscopy (as contrasted with roentgenography) in diagnosis of significant pulmonary tuberculous lesions varies from 13 to 35 per cent even in the hands of experts This fact must be borne in mind to avoid a false sense of security when relying on the fluoroscopic method alone

(3) Am Rev T be 45 1 14 J a 194

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[At present practically all candidates for enlistment and induction in the armed forces in this country are receiving x ray examination of the chest —Ed]

and the operation of the apparatus is relatively simple

The following factors favor roentgenoscopy and spot roentgenography (1) A small lesion may not be dense enough when it is close to the source of light (focal spot) to cast on the fluoroscopic screen or x ray film a shadow sufficiently intense to make its definition possible whereas the same lesion placed close to the screen or x ray film may cast a shadow which is readily visible (2) With a large focal spot tube a small lesion is less magnified than with the 1 5 mm focal spot tube (3) The milliamperage and kilovoltage can be varied to make a lesion more clearly visible which is of special value in studying the lungs in children Cases are presented which show the adequacy of the method and its advantage over the 14 × 17 in films both single and stereoscopic taken in the routine anteroposterior position

Diagnosis of Activity of Pulmonary Tuberculosis is according to Robert Davies (Nopeming Minn) a problem for the general practitioner and occurs occasionally in the practice of almost every specialist It is a problem because failure to appreciate activity may mean failure to forestall a long and disabling illness and even death while the misguided treatment of an inactive lesion means loss of time and money to the patient

Absence of clinical and laboratory evidence of activity is of no positive value in establishing a diagnosis of a stable tuberculous lesion X ray findings are the most important single factor in diagnosis The x ray film permits a definite diagnosis of active disease in absence of confirmatory evidence from clinical or laboratory findings Negative x ray evidence is of distinct value in arriving at a diagnosis of stable or inactive disease

In interpreting x ray evidence presence of effusion or cavity should be considered as indicative of activity There are three different radiographic pictures of tuber

(5) M i M 3 5 1 01 F bru ry 194

Since it has been shown that sensitivity to tuberculin following BCG vaccination reaches a certain height then falls off slowly higher concentrations were used in the older age group

The patch test was positive in 88 8 per cent of cases in which the Mantoux test was positive and negative in 100 per cent of those in which it was negative The reasonable agreement between the two tests indicates that the patch test gives positive reactions in individuals with a low grade sensitivity induced by an avirulent tubercle bacillus The fact that none of the children with a negative Mantoux reaction gave a positive reaction to the patch test indicates that a falsely positive patch test is as rare as a falsely positive Mantoux test An analysis of the cases in which disagreement was manifest showed no correlation with the age sex or race variant However when the technic was more or less standardized fewer differences appeared Careful cleansing of the skin with ether or acetone application of rather severe pressure over the actual patch areas with the thumbs and warming of the entire patch by placing the palm over the area for a minute or two seems the method of choice for best results Repatching is indicated before resorting to a Mantoux test to eliminate possible errors in technic in performance of the first test Readings on 114 patch tests at 48 and 96 hours after application suggested that accurate readings may be obtained best at 96 hours The patch test seems to offer an opportunity to surmount the objections to intradermal injection and can be used as a screening test to indicate positive reactors to tuberculin in children

Possible Significant Errors in Routine Tuberculin Tests Norman Rosenberg and Arthur C Allen[7] (New York City) point out that a method which uses a single syringe for diluting the tuberculin and for skin testing is open to many errors most of which act in one direction namely to make the final dilution stronger than

(7) J Lab & Cl Med 26 1650 J 1 1941

culous infiltration The first is the so called "soft" or exudative' lesion made up of small cottony spots or mottling of light density and with hazy and indistinct borders Such an appearance is not indisputable evidence of tuberculosis but is pathognomonic of an active lesion and as such is dependable The second type is made up principally of streaks or linear shadows with somewhat indistinct margins Any mottling present is more dense than in the first type of lesion and has more sharply defined borders With this type the roentgenologist may say that the disease does not appear entirely arrested but he cannot make a definite diagnosis either of activity or stability It may be possible with confirmatory clinical and laboratory data to make a definite diagnosis of activity To diagnose an inactive lesion with such an x ray appearance all clinical and laboratory data must be consistent with inactivity and the lesion must show no significant change over several years The third type of infiltration is that made up of fine stringlike sharply demarcated streaks and dense discrete and often calcified nodules In this type the roentgenologist may diagnose inactive or arrested disease with considerable accuracy but not with finality for even an apparently healed lesion may break down after years of stability All patients with tuberculous pulmonary lesions should have indefinitely repeated x ray examinations

Tuberculin Patch Test (Vollmer) on BCG Vaccinated and Control Children is discussed by I S Neiman Sol Roy Rosenthal and W G Motel[6] (Univ of Illinois) In 207 unselected consecutive children aged 3 months to 3½ years approximately half of whom were vaccinated with BCG at 4 to 7 days simultaneous patch and Mantoux tests were performed to determine the efficacy of the former The children came from a milieu with a high incidence of tuberculosis although their immediate family environment was nontuberculous

(6) J Pediat 19 540 544 October 1941

or an error of about 1 part in 75 The third factor is the human error which is greater with a finely graduated relatively poorly controlled instrument such as a syringe than with a pipet

The authors findings confirmed the impression of other workers who claim that individuals with active tuberculosis are far more sensitive to high dilutions of tuberculin than are positive reactors in the control groups While none of the clinically nontuberculous patients gave reactions to a 1 100 000 dilution (multiple pipet method) measuring 9 × 10 mm two with active tuberculosis reacted to high dilutions one to 1 100 000 and one to 1 50 000 On the other hand fully 64 per cent of nontuberculous patients reacted to a 1 100 000 dilution prepared by the single syringe method

It is suggested that either (1) purified protein derivative or (2) the multiple pipet method be used in the hospital in the preparation of weak solutions of tuberculin For the actual test different labeled syringes should be used for each dilution regardless of whether purified protein derivative or old tuberculin is used

Interpretation of Hemograms in Pulmonary Tuberculosis This study by W Stobie N J England and W H McMenemey[8] (Oxford England) was undertaken to assess the value of regular examinations of the blood in tuberculous subjects with special reference to prognosis The material studied consisted of 243 patients and 18 controls hospitalized on suspicion only of pulmonary tuberculosis The grouping of patients was based primarily on the Ministry of Health s classification (TB (−) TB +1 TB +2 TB +3) with further subdivisions into (1) uncomplicated effusion without roentgen evidence of parenchymatous disease of the lung and (2) lesions predominantly infiltrative and lacking in demonstrable excavation

The white cell counts taken on admission showed a count above 10 000 in only 5 per cent of the controls

(8) Am R Tuber 46 1 6 July 194

was actually intended To investigate this problem the following comparative tests were made On the skin of one forearm a 0 1 cc intradermal wheal was raised with a 1 100 000 solution of old tuberculin by the single syringe technic The other forearm was similarly and simultaneously injected with 0 1 cc of 1 100 000 solution of old tuberculin prepared in individual test tubes as follows 0 5 cc of O T + 4 5 cc of 0 9 per cent saline solution = 1 10 dilution 0 5 cc of 1 10 dilution + 4 5 cc of saline = 1 100 dilution etc A single standardized 5 cc pipet was used to deliver the saline but different 1 cc pipets were used for each dilution of old tuberculin and were marked so that they would not be used for other dilutions The amounts of solution were relatively large so that errors in measuring were thereby made minimal From results obtained in patients thus examined it could be readily seen that even a 1 10 000 dilution prepared by the 'multiple pipet method is weaker than the so called 1 100 000 dilution of the 'single syringe' procedure

The abnormal sensitivity of the single syringe method was found to be due first to affinity of tuberculin for glassware A comparison of dilutions prepared by the multiple pipet method was made with a similar set of dilutions prepared by using a single pipet throughout It was found that enough tuberculin adhered to the single pipet to increase irregularly the concentration of a given solution above its presumed potency The discrepancy between the single and the multiple pipet method was less than observed when the single syringe procedure was compared with the multiple pipet method The reason for this lies in the second error—the seepage of old tuberculin between barrel and piston By suitable measurements a formula was arrived at whereby the actual volume of fluid that seeps for a given distance between the barrel and the normally fitting piston could be calculated For the distance up to the 1 cc mark the seepage space was found to equal 13 cu mm

and the only significant improvements were in the single lobe neutrophils and sedimentation rate. In 32 patients in the group T B + 2 with good progress the only item in the hemogram that could be utilized for demonstration of improvement was the single lobe neutrophil. Of 47 patients in group T B + 2 with artificial pneumothorax only one third of the improved patients showed a definite change in the hemogram; for those deteriorating the results were still less constant and in 50 per cent of stationary patients the hemogram showed improvement. It was concluded that no reliance can be placed on hemograms regarding extent, seriousness or activity of the disease in any individual patient.

Secondary anemia was demonstrated in several cases. Its greater incidence in young adults (especially female) and middle aged patients suggests the desirability of estimating hemoglobin content of patients with tuberculosis and of actively treating any with levels below normal, especially females around puberty and the menopause. The findings also suggest careful search for tuberculosis in females in these age groups presenting symptoms of anemia.

[It is clear that the blood count as well as other so-called prognostic tests cannot be relied on to the exclusion of clinical, other laboratory and roentgenographic observation.—Ed.]

Electrophoretic Study of Blood Protein Response in Tuberculosis by means of the Tiselius technic was carried out in rabbits and humans by Florence B. Seibert and J. Walter Nelson[9] (Univ. of Pennsylvania). Serum was used rather than plasma to avoid the possibility of masking an antibody by the presence of fibrinogen. It was possible to establish a normal range for the various blood proteins and thus detect any variation from normal. The values found in rabbits during development of tuberculosis revealed that the percentage of albumin was lower than in the normal controls and gradually decreased with progression of the disease while the globu

(9) J. Biol. Chem. 143 29 38 March 194

This percentage however rose appreciably in the T B (—) and T B + 1 categories thereafter the increment was less steep until, in the T B + 3 group a quarter of them had a white cell count between 12 000 and 18 000 All mean readings of neutrophils in the clinical groups were above those of the controls and there was a steady rise from effusion' to T B + 3 as in the case of the total white cells The single lobe neutrophils and Bonsdorf count confirmed the tendency toward neutrophil leukocytosis with advancing disease for they showed a distinct shift to the left implying increased production of these cells Eosinophils and monocytes showed no significant alterations Lymphocytes showed a declining percentage and absolute counts with advancing disease It is suggested that the leukocytosis is the cause of the relative lymphopenia and inversely an improvement in lymphocyte percentage usually occurs because of restitution of the neutrophil count The mean sedimentation rate was increased in all the categories of pulmonary tuberculosis being considerably higher in the T B + 3 group than in the others It was noted that those with pleural effusions afforded the next highest average The Houghton index followed the general trend of the sedimentation rate but the coefficient of variation was smaller except in T B + 3

The progress counts showed that (1) improvement was associated with a falling single lobe neutrophil count and a rising Houghton index (2) It was felt that appreciable changes in progress hemograms should be associated with corresponding variations in the clinical picture if these hemograms are to be of any clinical value However there were so many inconsistencies that changes in the hemogram cannot be taken as definite evidence of clinical improvement (3) Appreciable changes in blood count were recorded in only about one third of the cases

On final counts in 16 cases with progress recorded as excellent the total leukocyte count had increased

studied In all the albumin was low and the α and γ globulins high (Fig 46) The X component also appeared whereas it was not present in normal human serums studied The one normal subject whose serum did show it was known to have been sensitized to tuberculin protein by constant contact with it There was also a suggestion that a high γ globulin may be associated with resistance to the disease One of the patients studied (first diagram of tuberculous serum in Fig 46) showed very high γ-globulin on the first test at which time he had been resisting extensive tuberculosis for three years At the time the second and third tests were made 5 months later he was reported doing poorly and the γ globulin was decreasing α globulin was increasing and the X component appeared

TREATMENT

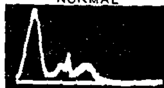
Voluntary Termination of Artificial Pneumothorax Review of 200 Cases is presented by George F Aycock and Paul E Keller[1] (Denver) The cases were classified according to the dominant tissue reaction present and the extent of the tuberculous lesion according to National Tuberculosis Association standards at the time artificial pneumothorax was induced namely exudative (179) caseous pneumonic (3) and fibrocavernous (18) Periods elapsed since completion of expansion range from 1 to 16 years

The condition of the patient and of the lesion under treatment as determined by the clinical course roentgen findings sputum analysis and erythrocyte sedimentation rate has been the prime factor in arriving at a decision to terminate the artificial pneumothorax The initiation of reexpansion was usually delayed until one year had elapsed after complete closure of cavities Likewise the patient had to be free from toxemia and in most cases from cough and expectoration In the case of the exudative group which cleared up leaving

(1) Am R T b 45 117 131 F b ry 194

lin percentage increased The first changes which oc curred were usually a rise in the *a globulin* fraction and the appearance of an unknown component desi nated X component especially if the disease progressed slowly Mobility of the X component was slightly great er than that of albumin It is worthy of note that this mobility is the same as that found under identical condi tions for a protein component in purified tuberculin protein suggesting that the tubercu lin protein may exist in the serum as such Furthermore the X component appeared regularly in normal rabbits after sensitization with tuber culin protein The percentage of *a* globulin always increased in normal rabbits after sen i tization to tuberculin protein and it could be shown that this was partly due to the tuberculin protein antibody Presence of this antibody however was not associated with immunity The increase of *a* globulin in patients with early tuberculosis may there fore be evidence of sensitiza tion to tuberculin protein One of the most constant re sults found during develop ment of tuberculosis was an increase in β globulin before death

NORMAL



TUBERCULOUS



TUBERCULOUS



TUBERCULOUS



F g 46—Hum n erums de l ing c rves La ge g mm glob l n seen in fl t di g m f t be cul u serum la t tw ums show prom t alph glob l a and X compo t ll xpo ures tak s 30 d g ee gl

Three patients with ad vanced tub were

expansion is even more clearly emphasized According to reactivation experience in the moderately advanced exudative series those under collapse for the shortest time fared better after complete reexpansion than those under collapse for longer periods This must not be interpreted as implying that the longer periods of collapse constitute a factor in the occurrence of reactivations for other factors must also be considered Cases showing signs of activity immediately on completion of reexpansion have never reached a state of arrest

There was no connection between the act of reexpansion and subsequent reactivations No case showed reactivation within less than 12 months following completion of reexpansion Most of the reactivations occurred at periods in excess of two years after completion of reexpansion The incidence and time of reactivations have in all essential respects been the same in this group of reexpanded pneumothorax cases as in those cases discharged from the same hospital as arrested or apparently cured without having received collapse therapy

Prolonged and indefinite periods of collapse under artificial pneumothorax present certain definite disadvantages There is likelihood of development of serious complications Pneumothorax of long standing with or without the complication of effusion sometimes shows marked thickening of the visceral pleura with the fixation of the collapsed lung resulting in the unexpandable lung Right cardiac hypertrophy and failure in such cases are of increased importance as a grave end result in chronic pulmonary disease associated with

little or no residuals, roentgen control of reexpansion was relatively simple However those cases leaving more in the way of fibrous residuals often showed various types of interlacing shadows, at times suggesting the presence of patent cavities In such cases roentgenograms from various angles, lateral and oblique and stereograms are a necessity The best aid in formulating an accurate estimate is serial roentgenograms at frequent intervals following institution of pneumothorax, combined with fluoroscopy before and after refills, the case should be followed up by the same physician or group of physicians The sputum specimens should be negative in direct smears for one year prior to completion of expansion When reexpansion is *almost complete* five more direct smears are examined and a culture made Recently, the authors have added the procedure of culture of stomach washings in cases showing apprec[illegible] [illegible]duals A low erythrocyte sedimentation rate [illegible] [illegible] m in 60 minutes is desired *Of more significance however* [illegible] ase on completion and consistently *lower in a given* [illegible] eatment was instituted *of treatment than that noted when* t[illegible] duration of

series and any interference with the action of the diaphragm carefully avoided in all prospective thoracoplasties The first series has remained practically unchanged for some years with 50 per cent good results Additional anterior rib resections were most common in the second series and were less frequently done in the third series The patients of the second series operated on between 1933 and 1935 show about 65 per cent good results but there was a definite deterioration in the figures toward the fifth year The third series of 126 patients operated on between 1936 and 1940 including 90 with thoracoplasty with apicolysis had a mortality rate of 3 17 per cent during the first two months and a total death rate to date of 6 35 per cent With the low mortality rate thus far with a definite reduction in complications especially postoperative flares and with a collapse obtained approaching the ideal of that afforded by a good pneumothorax there is reasonable hope for a substantial relative improvement in the third series when the fifth year is reached

Richard H Dieffenbach (Newark N J) and Anthony D Crecca (Verona N J) report on 100 consecutive cases of thoracoplasty with no operative mortality The patients were followed three to five years In this series 221 operations were performed Fifteen had only one stage at which time the first four ribs were resected Sixty five had two stages and 18 had three stages Twenty two revision operations were performed Results show that 71 cases are arrested with negative sputums and closed cavities and the patients are able to work 16 still have positive sputum and 13 died from progression of the disease It is concluded that thoracoplasty should be used when indicated and not reserved as a final resort for advanced cases Some form of plombage in the first stage is desirable and will maintain the negative status of the sputum in many cases Occasionally it will obviate the necessity for a second stage especially in bilateral cases Most

Hosp) present a study of collapse therapy, with special reference to thoracoplasty based on results of 13 years (1927 1939 inclusive) The material includes 241 patients treated by thoracoplasty and 19 treated by extrapleural pneumothorax Meticulous silk technic, careful hemostasis ether anesthesia with nitrous oxide and oxygen and postoperative administration of fluids were important features in the thoracoplasty procedure On the average three ribs were resected at the first stage and four ribs at the second with three weeks intervening *Since the fall of 1935 extrafascial apicolysis of Semb has been performed in over 90 per cent of all thoracoplasties exclusive of those for tuberculous empyema* Of the 241 patients 59 8 per cent are apparently cured, 4 6 per cent arrested 0 6 per cent apparently arrested 11 3 per cent quiescent 4 1 per cent unimproved 0 4 per cent worse and 15 7 per cent *dead* Of patients with empyema operated on 31 7 per cent are dead or twice the percentage of total deaths Of the total 38 deaths 11 occurred postoperatively 24 from tuberculosis not associated with the surgical procedure and 3 from incidental disease The rate of sputum conversion following thoracoplasty was 65 9 per cent A comparison of the two periods before and after adoption of apicolysis reveals that under this procedure the rate of sputum conversion is 16 per cent greater in the first six months following operation and 25 per cent greater in the first three months Four of the 19 patients with extrapleural pneumothorax died 7 are well and 8 are still in the institution

George F Skinner Lachlan Macpherson and Irene Allen (*Saint John N B*) *present a* comparison of three series of patients operated on during the past 17 years *Results suggest that the final judgment can* be given only after the fifth year following operation *In the first group operated on between 1921 and 1930* thoracoplasty was preceded by a phrenicectomy in many cases *This procedure was discontinued in the second*

erative Negative sputum (for at least six months) was achieved in 79 per cent of the entire series Of the total number 63 5 per cent have been discharged and of these 50 4 per cent are working or able to work

Thoracoplasty in bilateral pulmonary tuberculosis is discussed by Arthur M Vineberg, Douglas Ackman and Michael Aronovitch (Montreal) Of 100 patients 47 had bilateral active disease Results of thoracoplasty in these 47 patients are 42 5 per cent are well have negative sputum and are able to work 23 4 per cent are alive have a positive sputum and are either quiescent or slipping 34 1 per cent are dead Of 20 patients who showed retrogressing lesions in the contralateral lung at time of operation none died and 75 per cent are well Of 14 with progressive lesions on the contralateral side 65 per cent died and none are well and able to work It is concluded that the indications for thoracoplasty must be based not on the character of the disease in the contralateral lung—whether exudative or productive—but rather on the state of the disease—whether progressing or retrogressing

Results of 90 consecutive thoracoplasties are analyzed by Arthur H Aufses (Montefiore Hosp New York City) Every patient has been followed up There were 71 per cent arrested cases 18 per cent not arrested 7 per cent postoperative deaths and 4 per cent late deaths In 78 per cent of the patients who had a Semb extrafascial apicolysis the condition became arrested as against 66 per cent of those operated on without this technic Ninety five per cent of those discharged before Jan 1 1939 with condition arrested are working full time The rehabilitation and ability to earn a livelihood in these patients are due to cooperation of the phthisiologist thoracic surgeon and social welfare associations A careful study of the patients without arrest revealed the factors to be long standing disease with markedly fibrotic lungs containing numerous small cavities or a prolonged delay between the first and second

careful postoperative treatment with particular stress on promptly recognizing spontaneous pneumothorax and bronchial occlusion is important

George G Finney (Baltimore) reports study of 104 instances of thoracoplasty performed between 1937 and 1940 Cyclopropane gas preceded by seconal by mouth proved the most satisfactory anesthesia Proper position of the patient on the operating table to allow for good ventilation of the unaffected lung was secured by placing a pillow under the axilla A relatively normal level of blood pressure was maintained by giving whole blood transfusion during operation Incidence of superficial infection was almost eliminated by applying lanolin liberally over the closed wound before applying dressings Results are 42 3 per cent arrested cases 20 2 per cent apparently arrested 13 5 per cent improved 2 9 per cent unimproved 2 9 per cent not traced and 18 2 per cent dead Of the 19 deaths 6 were operative and 13 nonoperative

Herbert Meltzer (Ninette Manitoba) presents results of thoracoplasty in 181 patients performed in the five years preceding 1941 The operative procedure used was of the modern type as described by Alexander Number of ribs removed at each stage averaged three length of ribs removed was long Local anesthesia was used exclusively Operative and postoperative complications were few Contralateral collapse was well tolerated 80 per cent had negative sputum Best results were obtained in the age group 21 30 Most favorable results are found in the period from four months to four years after diagnosis Although the far advanced bilateral group had 73 5 per cent with negative sputum all deaths occurred in this latter group Acute cases showed less favorable results and higher mortality rate than other groups The less cavitation the better the results Of the 181 patients 166 are alive today Eight died of tuberculosis and seven of conditions other than tuberculosis Three of the deaths were op

tion between 17 and 32 mg per cent There was a con siderable variation in degree of acetylation in the same patient and from patient to patient This ran from a low of 2 per cent to a high of 28 per cent

The usual toxic reactions attributable to sulfanilam ide were observed in most patients Nausea and vomit ing were less severe with intravenous treatment than with the much smaller oral doses Chilliness and dyspnea were more frequent One patient developed gross hematuria possibly related to sulfanilamide Two pa tients had chills and fever the third day of intravenous treatment necessitating cessation of treatment In most patients fever increase in cough sputum and rales elevated sedimentation rate and leukocytosis associated with occasional chills and night sweats were observed during intravenous drip therapy

Of 13 patients 11 had at least five days of intravenous therapy Of these seven had one course of treatment without striking specific improvement Two patients with minimal pulmonary tuberculosis received two courses and showed slight resorption over 2½ months and 4 months respectively In one of these there was sputum conversion with two negative gastric cultures after the first course but four months later it became positive again In neither case was the improvement better than could be expected on bed rest alone Two patients received three courses One showed slight pro gression in the lesion of the left lung but simultane ously there was complete healing of an endobronchial tuberculous lesion The other patient exhibited some resorption of infiltrates in both apexes after six months and complete healing of a tuberculous pharyngeal ulcer in three months Permanent or complete sputum conver sion was not obtained in any case In three instances there were temporary improvement of the edema and infiltration of the tuberculous laryngitis during and for one or two weeks following sulfanilamide therapy Ultimately there was steady progression of these lesions

stage of the operation the delay usually being necessitated by a severe infection of the wound

[The increasing safety of the operation of thoracoplasty is one of the most striking recent advances in the treatment of tuberculosis This together with more effective procedures gives hope to an increasing number of invalids —ED]

Chemotherapy of Tuberculosis Sulfanilamide by the Intravenous Drip Method Gary Zucker Max Pinner and Harold Thomas Hyman[3] (Montefiore Hosp New York City) treated 13 patients with tuberculosis for 6 months to 15 years There were 2 minimal 1 moderate and 10 far advanced cases of pulmonary tuberculosis Extrapulmonary foci included tuberculosis of the larynx in three of the middle ear in two of the gastro intestinal tract in two and of the pharynx bronchus and genito urinary tract in one each Though most patients had exudative lesions and little or no tissue destruction a few with far advanced fibrocavitary tuberculous cases with little exudative disease were included The outcome in each patient was evaluated on the basis of the expectation of the future course of the disease on bed rest alone A time limit for therapeutic efficacy was set at about two months

An 0 5 per cent solution of sulfanilamide was used for the intravenous drip The solution was at first made up in 1/6 molar sodium lactate solution later normal saline was used as vehicle The drip was started at 9 00 a m and was continued 10 11 hours This was repeated on each of five successive days About 60 per cent of the total daily dose was given during the first few hours 0 18 0 2 Gm per K_g was administered the first day and 0 16 0 18 Gm per K_g on subsequent days After five days most patients were given small doses of sulfanilamide by mouth for five more days Total dosage for each course of treatment varied from 50 2 to 86 Gm The smallest daily dose intravenously was 7 7 Gm the largest 15 Gm During the drip administration it was possible to maintain blood concentra

(3) Am Re Tub 45 9 30 March 19

two of the 44 animals x rayed at six weeks showed definite diffuse miliary type mottling throughout both lung fields Eight animals showed shadows which were considered to be questionable and four were definitely negative X ray plates taken at 16 weeks showed complete disappearance of the previously demonstrated shadows in all but three animals and in these there was marked and almost total clearing On autopsy all animals were found to have grossly demonstrable pulmonary tuberculosis Arsenical therapy did not prevent the healing of extensive tuberculosis present in the animals There did not seem to be any measurable difference in the amount of tuberculosis present in the two arsphenamine treated groups one of which was infected with syphilis but the control group infected with both syphilis and tuberculosis which received no arsphenamine showed slightly but definitely more tuberculosis at section This would indicate that tuberculosis coexisting with syphilis runs a less benign course when the syphilis is not treated However since it is not known whether the presence of syphilis or the absence of arsphenamine is a factor it is more accurate to conclude that the tuberculosis in the treated animals fared no worse than in the controls

Ether Anesthesia in Presence of Pulmonary Tuberculosis The current prejudice against ether anesthesia for operations on tuberculous patients is not founded on study and careful record keeping but is mainly based on articles written one to three decades ago when ether was administered by the open cone or open drop method Henry K. Beecher and Ralph Adams (Massachusetts Gen l Hosp) report on five years experience with patients who received closed ether anesthesia notwithstanding their pulmonary tuberculosis The series included 147 patients who underwent 260 thoracoplasties

The apparatus used for ether anesthesia consists of

(5) J A M A 118 1 041 [illegible]

Improvement was attributed to the clearing of secondar pyogenic infection Two other mucosal lesions healed during treatment a pharyngeal ulcer in 3 months and a caseous endobronchial lesion in 3½ months

[While encouraging results in animal experimentation have been obtained by the use of sulfonamide drugs by various workers experience in clinical use of these agents has not as yet convinced observers that the effects are striking or different from those obtained by rest treatment alone —Ed]

Effect of Arsphenamine on Tuberculosis in Syphilitic Animals is reported by Walsh McDermott Bruce Webster and Donald Macrae[4] (Cornell Univ) Fifty rabbits which had previously had chest x ray films and blood Wassermann tests were inoculated intravenously with 0 5 cc of a suspension containing 0 25 mg bovine type tubercle bacilli (B1 Saranac Laboratory) Two weeks later all gave positive reactions to intradermal injections of old tuberculin Blood Wassermann tests were repeated and 32 animals were inoculated in the right testicle with Spirochaeta pallida Three weeks after inoculation of syphilis or six weeks after inoculation with tubercle bacilli the animals were divided into three groups groups I and II were composed of animals with both tuberculosis and syphilis group III of animals with tuberculosis alone The animals of groups I and III received old arsphenamine in doses of 10 mg per kg per week for 10 weeks Eight weeks after infection with syphilis all 14 of the treated animals and all 15 of the tuberculous nonsyphilitic group gave negative Wassermann reactions while of the 13 untreated syphilitic animals there were four positive reactions one doubtful positive reaction and eight negative reactions One of the eight with negative reactions showed a positive reaction and two showed doubtful positive reactions at 16 weeks

Chest x rays were taken again at 6 weeks and at 16 weeks after inoculation with tuberculosis i e before and after the 10 weeks of arsenical treatment Thirty

(4) Am. Rev Tub 44 504 51x N [illegible]

two of the 44 animals x rayed at six weeks showed definite diffuse miliary type mottling throughout both lung fields. Eight animals showed shadows which were considered to be questionable and four were definitely negative X ray plates taken at 16 weeks showed complete disappearance of the previously demonstrated shadows in all but three animals and in these there was marked and almost total clearing On autopsy all animals *were found to have grossly demonstrable pulmonary tuberculosis* Arsenical therapy did not *prevent* the healing of extensive tuberculosis present in the animals There did not seem to be any measurable difference in the amount of tuberculosis present in the two arsphenamine treated groups one of which was infected with syphilis but the control group infected with both syphilis and tuberculosis which received no arsphenamine showed slightly but definitely more tuberculosis at section This would indicate that tuberculosis coexisting with syphilis runs a less benign course when the syphilis is not treated However since it is not known whether *the presence of syphilis or the absence of arsphenamine is a factor it is more accurate to conclude that the tuberculosis in the treated animals fared no worse* than in the controls

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The apparatus *used for* ether anesthesia consists of

(5) J A M A 118 1 011 09 Ap 4 194

a closed system with carbon dioxide absorption Following a brief nitrous oxide oxygen induction ether is administered with a high percentage of oxygen Use of intratracheal tubes is avoided except in cases of unusually abundant sputum because of danger of spreading tuberculous infection in the areas of slight trauma to the airways Of 126 patients subjected to thoracoplasty between 1935 and 1939 8 died early (6 3 per cent) that is within the arbitrary two months period after operation and 8 later (6 3 per cent), making a total death rate of 12 7 per cent from tuberculosis in any form and from causes directly or indirectly connected with the operation 59 5 per cent were apparently cured and in 8 7 per cent the process was arrested in 1 6 per cent apparently arrested and in 14 3 per cent quiescent These results compare favorably with those from other clinics where ether is not used or used rarely

In the authors opinion the anesthetic agent is not important in these cases as long as it permits the use of sufficient oxygen and allows the surgeon to carry out an unhampered and unhurried operation It is important to choose an anesthetic agent which depresses vagal activity when thoracic surgery is contemplated and ether excels other agents in this regard Several of the newer anesthetic agents appear to have a death rate in general surgery two or three times that of ether which is well tolerated by very sick patients

[Anesthesia of any type may have an adverse effect in the patient with open cavitary tuberculosis unless adequate precautions are taken in timing the operation in promoting drainage of the cavities beforehand and afterward in guarding against aspiration and in shortening the operation as much as possible The harmful mechanism involved seems most often to be the transbronchial spread of the infection into healthy parts of the lung Beecher and Adams refer to this in their article —Ed]

COMPLICATIONS

Tuberculosis of the Ear and Mastoid in Adults Sumner S Cohen and Gerald W Koepcl e[6] report on 140

(6) Am R Tube c 4 4 7 436 Ap 1 194

cases of tuberculous otitis media seen at the Glen Lake (Minn) Sanatorium between 1924 1941 Patients were aged 14 68 50 per cent were adults aged 30 or less The condition was unilateral in 124 cases and bilateral in 16 With the exception of two all patients had active pulmonary tuberculosis 84 1 per cent had far advanced 15 2 per cent moderately advanced and 0 7 per cent minimal pulmonary tuberculosis Pulmonary cavitation was present in 94 2 per cent Two patients had extra pulmonary tuberculosis without associated active pul monary tuberculosis Extrapulmonary tuberculous foci also were present in 55 8 per cent of the remaining patients Of the entire series 62 died 57 were dis charged with the pulmonary lesion considered arrested in most and 21 were still under treatment The data indicate that tuberculous otitis media is a local manifes tation of a serious constitutional disease

At the onset there is a sense of fulness in the affected ear with rapidly developing loss of hearing Buzzing ringing throbbing humming or crackling often fol lows and pulsations are not uncommon Aural dis charge serous and scant at first but rapidly becoming purulent (occasionally thick and cheesy) appears a few days to a few weeks after onset of early symptoms Absence of severe pain is of diagnostic importance but presence of pain does not entirely eliminate tuberculosis Early changes consist of inflammation of Shrap nell's membrane extending inferiorly along the handle of the malleus This inflammation increases rapidly so that within a few days the entire tympanum is inflamed and edematous The perforation is small at first but later a large portion of the drum may be destroyed Polypoid fleshy and easily bleeding granulations are common Hearing tests reveal a moderately severe deaf ness usually of the obstructive type

The most reliable single diagnostic aid is inoculation of the aural discharge into a guinea pig In over 80 per cent of cases diagnosis was made by this method

With the exception of one instance of facial paralysis there was no clinical evidence of involvement of the mastoid process Roentgenograms of the mastoid process revealed involvement in 90 of 92 patients with unilateral disease so studied of 13 with bilateral otitis media 11 showed bilateral and 2 unilateral involvement of the mastoid Tuberculous mastoiditis could not be differentiated from any other inflammatory reaction of the mastoid Tuberculosis of the petrosal bone was found in 10 cases at autopsy

The authors believe that sputum infected with tubercle bacilli reaching the ear through the eustachian tube precipitated the otitis in most cases Surgery appeared to be the precipitating factor in five cases since four occurred shortly after thoracoplasty and one apparently hematogenous followed removal of a tuberculous appendix

Included among complications were miliary tuberculosis with meningitis (possibly due to pulmonary involvement) in two cases facial paralysis in one mild vertigo in a few and tuberculous abscess of the temporal bone in two Excluding mastoiditis, serious complications are uncommon with tuberculous otitis media of adults

Treatment consists of dry cleansing local heliotherapy and insufflation of a powder consisting of 25 per cent potassium iodide in boric acid Myringotomy is not advised in the acute congestive stage Myerson and Gilbert list the following indications for radical mastoid surgery in tuberculous mastoiditis subperiosteal abscess circumscribed labyrinthitis facial paralysis persistent postauricular fistula after simple mastoidectomy mastoid tenderness and headache associated with profuse discharge Complete healing apparently take place in over half of the cases and is largely dependent on the patient s general resistance to tuberculosis In 68 per cent of cases complete healing occurred without perforation of the tympanum or any demo rable dis

charge Prognosis for tuberculous otitis media per se is serious only as it affects the hearing not as it concerns life expectancy

[The occurrence of a painless discharge from the ear should always lead to the suspicion of tuberculosis and a search for pulmonary disease —Ed]

Tuberculous Esophageotracheobronchial Fistulas are very rare according to José L. Monserrat [7] who has observed only 3 such cases among 215 autopsies of tuberculous children and none in much more adult material In a collected series of 681 cases of aero digestive fistulas Mangabeira Albernaz found only 14 of tuberculous origin Since tuberculosis of the esophagus is uncommon it is rarely the cause of perforation and fistulization Although more common tracheobronchial tuberculosis is likewise not a frequent cause of fistula formation Tuberculous ulcers situated in the upper third of the trachea in extension of tuberculous laryngitis or ulcers of the large bronchial branches associated with tuberculosis of the lower third of the trachea may extend into the depth denude and necrotize the cartilaginous rings give rise to peritracheitis and adhesions and ultimately perforate into the esophagus Most often tuberculous esophageotracheobronchial fistulas owe their origin to tuberculosis of the mediastinal lymph nodes The associated periadenitis may produce adhesions around the esophagus and traction diverticulae into which the softened contents of the glands may become evacuated thus perforating the trachea or bronchi and forming an esophageotracheobronchial fistulous tract

All three cases reported by Monserrat occurred in children during the florid stage of the primary condition as result of massive infection or of conditions which caused the tuberculous disease to run an accelerated evolutionary course (early dissemination of Huebschmann) It is therefore concluded that the possibil

(7) A b ro g t d n t s m y p t 46 55 A g t 1940

ity of aerodigestive fistulization is greatest during the period of primary infection or the early stages of secondary tuberculous involvement, i e, during the time of marked exudative tendency and lymphoglandular preponderance

Tuberculous Cervical Adenitis H Matuno[8] made a detailed study of the tonsils and other lymphoid tissues of the neck in 60 patients The hematogenous nature of tubercle formation in these tissues was evidenced by the fact that the earliest stage of the tubercles was seen at the terminal branches of arterial ramifications as well defined nodules in either the cortex or the medulla limited by the sinuses Favoring the theory of lymphogenous origin of tubercle formation was evidence of various degrees of exudative inflammation at the marginal, interstitial and medullary sinuses of the lymph nodes *in response to the tubercle bacilli* or their catabolic products which entered the nodes by way of the afferent channels In the tonsil the hematogenous *infection was usually found localized* either within the lymphoid follicles or in their neighborhood in the form of miliary tubercles which tended to undergo healing fibrosis Little evidence was found of lymphogenous infection in the tonsil such changes as had occurred from lacunar epithelium tended to undergo necrosis making probable the spread of the disease to the interfollicular tissues In individuals without evidence of localized and well defined tuberculous infection in the respiratory or gastro intestinal tract microscopic study of the cervical lymph nodes often demonstrates the presence nature and extent of the disease Information derived from these studies also suggests the probable tuberculous nature of the disease of the organs and tissues served by the lymphatic tissues under consideration Tuberculous cervical adenitis may though rarely, occur during the generalized stage of Aschoff and Ranke, not only by way of the blood stream but more often by the

(8) Kekkaku 19 709 36 March 1941

lymphatics from the hematogenous focus in the lymphoid tissue Retrograde lymphogenous infection of the cervical nodes from the tuberculous nodes in the supraclavicular areas rarely occurs

Bilateral Tuberculous Pleural Effusions A Study of 45 Cases observed in the last 20 years in Manitoba Sanatorium is presented by Alfred L Paine[9] In none of the cases was a pneumothorax present Tubercle bacilli were isolated from pleural fluid without guinea pig inoculation in 26 6 per cent and sooner or later from some part of the body in 48 8 per cent of the whole series Most of the patients had little or no pulmonary involvement at onset being admitted for pleurisy rather than pulmonary tuberculosis However subsequently in 47 per cent pulmonary disease appeared or increased while in 38 per cent tuberculosis involved other organs In some instances both pulmonary and nonpulmonary disease appeared in the same individuals so that of the whole group 56 per cent showed further manifestations of tuberculosis and 44 per cent have so far remained free Over half the patients were in the decade from 15 to 24 58 per cent were females and 42 per cent males Males showed a higher incidence of complications and a higher mortality rate At present 47 per cent are well 22 per cent are under treatment and 31 per cent are dead

A survey of the cases indicates that the prognosis of bilateral tuberculous effusion is poor and that the disease is distinctly more malignant than unilateral effusion Prognosis seems almost as bad with a considerable interval between effusions as when they occur simultaneously or close together Apparent absence of lung involvement at onset did not give a more favorable prognosis and adequate treatment had less effect on end results than in unilateral effusion Considering the frequency of miliary lung disease and involvement of other organs such as spine kidney adrenals lymph

(9) Am R T be 44 4 438 O t ber 1941

nodes and meninges where the mode of infection i
conceded to be through the blood stream it must be con
cluded that bilateral effusion is usually a manifestation
of hematogenous infection and not infrequently of gen
eralized miliary tuberculosis The dominant factor in
the production of these effusions seems to be allergy

DISEASES *of the* BLOOD *and* BLOOD-FORMING ORGANS, DISEASES *of the* KIDNEY

GEORGE R MINOT MD SD FRCP
(Edinburgh and London)

AND

WILLIAM B CASTLE MD SM
MD (Hon) Utrecht

PART III

DISEASES OF THE BLOOD AND BLOOD FORMING ORGANS

GENERAL CONSIDERATIONS

The articles in this section are concerned with certain general aspects of blood dyscrasias and especially because of their current importance in military medicine various aspects of blood transfusion and the use of blood substitutes —Ed

Hereditary Factors in the Blood Dyscrasias Thomas B Cooley[1] (Detroit) states that many blood dyscrasias have a definite hereditary background while in others a hereditary role is problematical The condition most indubitably linked with heredity is hemophilia With the exception of the perennial question regarding female hemophiliacs its sex linked heredity is generally understood While sex linked heredity in disease is not uncommon there is only one other blood dyscrasia in which it is present namely a special type of elliptocythemic anemia [Both sexes are affected in most reported studies of elliptocythemia See the following article —Eds] This suggests that diseases the inheritance of which is dependent on genes located in different chromosomes may have their primary effects on different tissues Current theory regarding the clotting mechanism suggests that the defect in hemophilia is in the plasma in which case there need not be assumed any such connection with the reticulo endothelium as seems evident in a number of the other dyscrasias

Congenital hemolytic icterus elliptocytosis and the sickle cell trait clinically and genetically form a fairly definite group Elliptocytosis has generally been considered a curiosity without special pathologic interest

(1) Am J D Child 6 18 J l 1941

Recent reports however indicate a not uncommon association of elliptocytosis with a disease state which parallels hemolytic icterus almost exactly with the single exception of the substitution of the elliptic cell for the spherocyte On the other hand the frequent occurrence of elliptocytosis without symptoms and resemblance of the elliptic cells to those of the sickle form suggest a relation of the three conditions There are of course definite differences Heredity is dominant in all three and the consensus is that the cells do not take on their peculiar shape until they reach the reticulocyte stage This may mean that mutations occur in the same gene

The problem of heredity in pernicious anemia is more complicated Evidence of an unusually high incidence in certain families suggests an hereditary factor Gastric anacidity is likewise common in such families and possibly with it a lack of Castle s intrinsic factor Curiously enough idiopathic hypochromic anemia may develop in the same family and even in the same patient To confuse the issue further gastric cancer occurs in such families with suspicious frequency Heredity studies in these conditions are difficult since the diseases become manifest in adult life at which time it is difficult to investigate antecedents or relatives Sole recourse may then be had to several theories, ranging from that of inherited gastric inferiority, which permits environmental factors to cause the disease to develop to the bald statement that the same mutant gene is responsible for all three diseases again with environmental aid or the weak suggestion that two genes may be involved one affecting the stomach and the other the bone marrow So far as pernicious anemia is concerned there is not much doubt that anacidity and probably absence of the intrinsic factor are often its hereditary precursors Enough data are not available to determine whether the trait for pernicious anemia is dominant or recessive It does not seem to be sex linked

Elliptic Erythrocytes in Man Helen Wyandt Paul M Bancroft and Theodore O Winship (Univ of Nebraska) report 86 new cases of elliptocytosis in three large families of German extraction The morphologic change takes place during or after the reticulocyte stage in the development of the red blood cell The cause is unknown Inheritance is probably as a simple mendelian

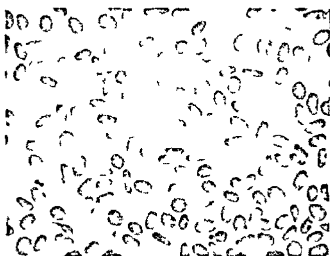


Fig 47 —Ell pt r d ll n bl d of h lthy rr

dominant trait The trait was more common in males than in females One member of each of two pairs of twins had elliptic cells while the other had round ones In one of the families both father and mother had elliptic cells in large numbers One subject presented laboratory and clinical evidence of both elliptocytosis and spherocytosis The fact that all other members were free from anemia unusually healthy and long lived lends support to the opinion that the anomaly has no definite relation to disease

(2) A h Int M d 68 1043 106 D mb 1941

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to consist of a bimolecular layer of lipoid molecules be tween two layers of protein molecules This refutes the concept that proteins must be reduced to their amino-acid constituents before passage through the cell mem brane

Figure 48 illustrates certain features of protein metab olism The liver is considered to be strategically sit uated and of sufficient size to perform most of the work of protein synthesis Many plasma proteins emerge from the liver cells and can be used in the body to supply all or most of its protein requirements Liver cells can store protein and can give out stored protein or fabricated protein The protein on its way out or in is designated transition protein which by cleavage and reassembly through ferments is on its way to cell protein or to plasma protein Much cell protein cannot be removed and is called indispensable Parenchymal cells or tissues can act to store proteins to use proteins or to release stores and perhaps to fabricate protein in a small way Hemoglobin in its production may draw on the plasma protein but hemoglobin stands apart in the protein economy and does not contribute freely to the protein pool On the other hand the body guards jealously the fabrication of hemoglobin and given a real need for both plasma protein and hemoglobin the protein flow favors hemoglobin which under these cir cumstances is always produced in more abundance than the plasma protein

The Effect of Age on Susceptibility of the Erythro cyte to Hypotonic Salt Solutions has been determined experimentally by W O Cruz P F Hahn W F Bale and W M Balfour[5] (Univ of Rochester) When radio active iron is administered in a single dose to a dog in which there is a stimulus for hemoglobin formation the isotope is promptly incorporated into the pigment in the red cell Cells thus identified by their radioactivity can be regarded as of known age and then be compared

(5) Am J M S 0 15 163 A gu t 1941

Hemoglobin and Plasma Proteins Their Production Utilization and Interrelation G H Whipple[4] (Univ of Rochester) summarizes present concepts of plasma protein metabolism Food proteins yield the amino acids absorbed from the intestinal tract and the amino acids are synthesized in the liver cells and elsewhere into plasma proteins These plasma proteins and amino-acids supply the protein requirements of the body cells. Normally, there is a considerable reserve of plasma pro-

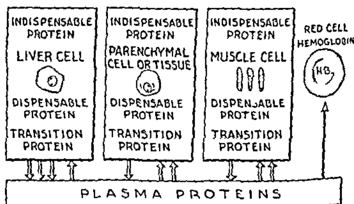


Fig 48

tein forming material (one to five times the circulating mass) which reserve may be reduced by fasting low protein diet or plasma depletion This depletion of protein reserve lowers the body resistance to infection and intoxication These body protein stores protein production and protein wear and tear are in a state of dynamic equilibrium The proteins can pass readily from plasma into cells and the reverse without loss of nitrogen Passage of proteins through cell surfaces is thought to occur by preliminary absorption of the protein on the cell membrane modification of the protein by ferments contained in the membrane with consequent ultimate passage through the membrane which is thought

(4) Am J M S 203 477 489 Apr 1 194

would appear like a target when viewed on the broad surface That this is actually the shape of the cell can be seen by oblique illumination of dry smears or in bas relief photographs (Fig 49) Atypical variations are seen in every smear The central stained mass may be

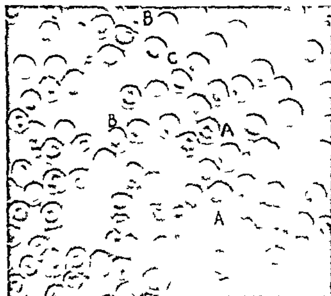


Fig 49—B l f phot mi gr ph of t get ell m d by p i t ng th o gh supe mp ed po t nd n t films A t get ll B bowl shaped ll C t rm d t t g C ll wh h a nt n b wl h pe n dry sm a Co l p dry m Wright t

joined to the outer rim by a bar of varying thickness or a ridge may cross the center of the cell with a thick ened central dot

No target cells are seen in wet preparations Instead an equivalent number of cells appear as shallow or more uncommonly deep bowls or cups Rarely the bowl shape is preserved in the dry smear (*B* in Fig 49) When blood is diluted with hypotonic salt solutions the

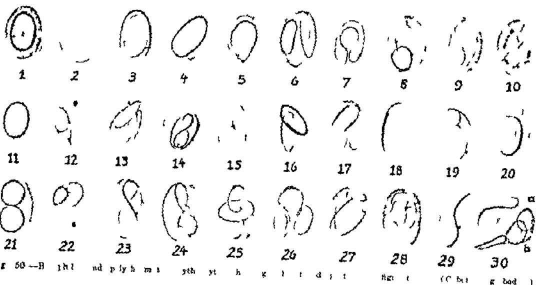
with those of the general run of cells of the circulation as concerns susceptibility to hypotonic saline The very new cells in the circulation (less than 4 days of age) are found to be markedly less resistant to the hypotonic salt solution than are the other older cells This difference in susceptibility disappears after three to four days There is also an indication that possibly the very old red cells (130 days) are more resistant to hypotonic saline than the circulating cells of the mean age group

Significance of Target Cells in Anemia Milton G Bohrod[6] (Miami Beach Fla) believes that the target cell is a newly formed cell produced by the bone marrow in response to blood loss, regardless of cause Rather than being uncommon target cells frequently appear in the stained blood film They can be found in small numbers up to 1 to 2 per cent early in most cases of anemia Rare ones may even sometimes be seen in apparently normal smears In more chronic anemias the number is variable but they may be found rangin from 1 to 10 per cent in many cases

Presence of target cells in stained smears is transitory in acute anemia Often they disappear before there is a significant elevation of the erythrocyte count, therein resembling the reticulocyte They may be present for only one to two days rarely for a week and in most cases they are seen for four to five days They usually appear three to four days following moderately severe hemorrhage and coincident with their appearance there is a transitory decreased fragility of the erythrocytes

Target cells are usually of normal diameter In the stained smear they are made up of a rim of hemoglobin containing material and a central hemoglobin containing area the two areas being separated by a zone which is clear unstained Barrett conjectured that this appearance was due to a central knoblike projection in a bowl shaped cell and showed that a body thus shaped

(6) Am J M Sc 0 869 8 4 Dec 1941


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proportion of bowl shaped cells (or of target cells in dry smears) increases as the salt concentration decreases This is due to the hemolysis of the normal cells and the preservation of the target cells, most of which resist hemolysis in 0 3 per cent sodium chloride The target cells are resistant to acetic acid in concentrations which destroy normal cells

There is little reason for assuming that the target cell is a fundamentally deficient cell in any type of anemia Their frequency in Cooley s anemia is no greater than in cases of sickle cell anemia or of acute hemorrhage Their common occurrence in the early phases of blood regeneration does not indicate that the target cell is congenitally malformed in the same sense as the sickle cell elliptical cell or spherocyte The target cell is merely a hyperresistant young cell appearing following blood loss If the loss is chronic the cells may be present constantly and in large numbers Its occurrence is analogous to that of the reticulocyte which also appears in the early phases of erythrocyte regeneration and has practically disappeared as normal red cell count is reestablished

Ready acceptance of this simple concept of the target cell is blocked by the oddity of its shape Why should blood regeneration be associated with a change of shape of the erythrocyte? Assuming that the cell does not change its shape in vivo it is possible to explain the appearance of the target cell Thus since the normal shape of the circulating erythrocytes is unknown and because much evidence suggests that they are really convex concave disks it is possible but not yet proved that the target cell preserves the bowl shape of the intravascular cell in modified form and resists deforming influences which are responsible for producing the biconcave disk seen in blood outside the body

Origin and Nature of Cabot Ring Bodies of Erythrocytes Cabot described red and blue staining circular and twisted bodies in basophilic polychromatic and

in plasma volume The plasma volume then gradually increased until after three to four days it was greater than the original plasma volume by an amount approximately equal to the volume of red blood cells removed In the three subjects who did not receive saline solution determinations of plasma volume were performed 36 111 minutes after hemorrhage During this period the plasma volume increased only 145 230 cc although 760 1 070 cc blood had been removed In none therefore was there a sudden large increase in plasma volume following hemorrhage

Immediately after hemorrhage the total circulating protein was diminished by approximately the amount of protein removed during venesection In the first two hours after bleeding increase in plasma volume was accompanied by a decrease in serum protein concentration and by only a slight increase in total circulating protein In the three subjects in whom plasma volume was determined within two hours after hemorrhage the average addition of protein to the plasma was only 5 Gm This initial increase in plasma volume therefore was the result of addition of a protein poor fluid to the blood stream In the three subjects who did not receive intravenous saline this initial period of dilution was completed in less than two hours Thereafter the serum protein concentration did not change or increased slightly This means that after the initial period of dilution the increase in plasma volume was accompanied by a simultaneous increase in total circulating protein As protein and fluid were added to the blood at the same time the protein concentration did not fall as the plasma volume increased

In two of the three subjects given saline solution the results were similar During and after administration of the fluid there was a sharp drop in protein concentration although never to the level to be expected if all the solution had been retained in the vascular system There was a corresponding drop in hematocrit readings During the three hours after saline administration the serum

glacial acetic acid method which modify permeability of the cell envelope replicas of Cabot ring bodies were produced in normal mature erythrocytes but not in normal erythroblasts Creation of the bodies depends on the physicochemical state of the lipoproteid colloids at the various maturation stages in erythroblasts the colloids may be in a transition stage and thus not able to form Cabot ring bodies

[The following three articles deal with the physiology of acute blood loss a subject which concerns both the patient and the donor in connection with transfusions —Eds]

Response of Normal Subjects to Acute Blood Loss is described by Richard V Ebert Eugene A Stead Jr and John G Gibson II[8] (Harvard Univ) In six subjects 760 1 220 cc blood (15 5 19 7 per cent of the blood volume) was removed in 6 to 13 minutes Three were given 1 000 cc physiologic solution of sodium chloride immediately after venesection Circulatory collapse developed in five the sixth had no symptoms None complained of any symptoms until near the end of venesection though moderate pallor cool hands and slight sweating of the forehead appeared Onset of collapse was sudden occurring in two while the blood was being taken and in three in one to four minutes after venesection was completed In four subjects arterial pressure and heart rate were carefully followed Before onset of collapse there was only slight fall in systolic pressure (average 11 mm Hg) while the diastolic pressure remained unchanged the heart rate increased 14 30 beats above basal level With onset of collapse both systolic and diastolic pressure fell precipitously and the heart beat became strikingly low between 36 and 40 beats per minute The subjects complained of weakness nausea a sensation of weight on the epigastrium and blurred vision An ashen gray pallor developed and they retched perspired profusely and responded slowly if at all to commands One subject became unconscious

Immediately after hemorrhage there was a sharp drop

(8) Arch Int Med 68 578 590 Sept

555 cc This drop is not sufficient to be dangerous or to produce more than transient symptoms Average time required to replace this amount of hemoglobin was 50 days with a smaller donation and a smaller drop in hemoglobin content the *recovery period* was shorter Longer recovery periods were associated with a greater *drop in hemoglobin content and could not be correlated* with the initial blood hemoglobin values Hemoglobin was regenerated in men at the rate of 0 049 Gm per 100 cc blood per day with a normal intake of dietary iron without medication In women under these conditions the increase was 0 040 Gm per day

Subsequent donations may be given with safety as soon as the hemoglobin content has returned to its original level An interval of three months should be allowed *between blood donations if the donor's hemoglobin* content is not determined regularly However in 74 2 per cent of this series *two months sufficed for regeneration* The rate of hemoglobin regeneration after subsequent *blood donations did not seem to be slower than* after the first donation Administration of 1 Gm iron and ammonium citrates daily increased the daily hemoglobin regeneration by 49 per cent and shortened the recovery period from 49 to 35 days during the first period of its administration It had progressively less effect after subsequent blood donations Because of the slower regenerative power of their blood *female donors should* be allowed longer intervals between blood donations

Blood Plasma *is discussed by Max M Strumia and* John J McGraw (Bryn Mawr Pa Hosp) with special consideration of problems of preservation *Regardless* of the means of preservation used plasma must be safe from the standpoint of (1) bacterial contamination (2) presence of flocculent protein precipitates and (3) unusually high iso agglutinin titer The manner of preservation greatly influences the survival of various specific elements of plasma Preservation in the liquid state at room temperature (approximately 77 F) causes little

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protein concentration and hematocrit readings rose indicating that fluid was leaving the blood stream After this period the serum protein concentration remained approximately constant while the hematocrit reading fell showing that both fluid and protein were being added to the blood stream Values for plasma volume determined 3½ and 5 hours after fluid administration were still 2?0 and 370 cc respectively lower than the prehemorrhage level In the third subject the dilution lasted much longer Five hours after hemorrhage the plasma volume was higher than the original prehemorrhage value and the lowered serum protein concentration showed that considerable dilution was still present

At varying periods after hemorrhage the red cell volume was estimated from the plasma volume and hematocrit reading In the three in whom blood volume was measured within two hours after hemorrhage before there was much change in hematocrit value the predicted and determined red cell volumes agreed closely (average difference 1 9 per cent) After dilution had occurred and the hematocrit level fallen the predicted and determined red cell volumes no longer agreed The latter was lower than the former in five subjects In the sixth they were the same The difference in any one case was too small to be significant but since the discrepancies were always in the same direction that trend was believed to be significant Likewise the red cell volume determined shortly after hemorrhage was always 5-12 per cent higher than that determined three days later Apparently the total red cell volume cannot be accurately calculated from the plasma volume and hematocrit readings because the cell plasma ratio in large and small blood vessels is different

Rate of Hemoglobin Regeneration in Blood Donors In a study of the drop in hemoglobin content which follows a blood transfusion Willis M Fowler and Adelaide P Barer[1] (State Univ of Iowa) found in 200 donors an average drop of 2 3 Gm after removal of

(1) J A M A 118 4 1-4 7 Feb 7 194

500 cc This drop is not sufficient to be dangerous or to produce more than transient symptoms Average time required to replace this amount of hemoglobin was 50 days with a smaller donation and a smaller drop in hemoglobin content the recovery period was shorter Longer recovery periods were associated with a greater drop in hemoglobin content and could not be correlated with the initial blood hemoglobin values Hemoglobin was regenerated in men at the rate of 0 043 Gm per 100 cc blood per day with a normal intake of dietary iron without medication In women under these conditions the increase was 0 040 Gm per day

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or plasma is hastened and intensified when the red cell are suspended in a high salt concentration Agglutina tion may be inhibited when unheated and stored serum is used although no visible hemolysis is detectable Heat ing to 55 C alters the serum proteins which in unheated serum inhibit antibody reactions Similarly, higher salt concentrations stabilize the labile globulins and allow flocculation to take place The increased salt concentra tion intensifies both the strength and the speed of aglu tination (see Table) Incubation at 37 C further enhances the effect Equal amounts of the red cell sus pension and serum or dilutions of serum in isotonic salt solution are used

EFFECT OF SALT CONCENTRATION ON AGGLUTINATING ACTION OF UNHEATED SERUM (GROUP 0) ON B RED CELLS

SERUM DILUTION	ACTION AT ROOM TEMPERATURE ON RED CELLS SUSPENDED IN					
	0 9% NaCl			3% NaCl		
	At 2 Min	At 15 M	At 1 H	At 2 Min	At 15 M	At 1 Hr
Undiluted	—	+	+	+++	++++	++++
1 2	—	+	+++	+++	++++	++++
1 4	±	++	+++	++	++++	++++
1 8	—	++	+++	+	++++	++++
1 16	—	+(+)	+++	—	+++	+++
1 32	—	+	+++	—	+	++
1 64	—	±	++	—	—	+
0	—	—	—	—	—	—

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e increased salt concentration however is itself le of inhibiting agglutination especially in higher dilutions Although the speed and strength of ation are at first much increased the end titer

is generally successful This procedure makes it possible to avoid the false negative reactions caused by inhibition of agglutination or hemolysis which may occur in the examination of unheated serum in blood grouping particularly in cross matching tests

Globulin Fractions of A and B Agglutinating Serums for Blood Typing William Thalhimer and Sophronia A Myron[8] (New York City) report that blood group specific iso agglutinins for determining blood types can be greatly concentrated by the usual method of globulin fractionation with sodium sulfate The globulin fraction is concentrated four to six times the original pooled serum To some fractions 0 25 per cent phenol and 1 20 000 merthiolate were added and others were prepared without preservative Both were found satisfactory The preparations were clarified by passing through a Buchner funnel containing paper pulp and filtercel and then through a clay filter which holds back bacteria The final sterile vialed material has not deteriorated when kept at plus 5 C for at least six months Preparations are easily obtainable which show detectable macroscopic agglutination of red cells in 5 seconds with the formation of large clumps within a period of 20 to 30 seconds

Fig 4—P ym r cn d T t t n l m n l t re used f blood gr up (Th h mer Myr)

The authors describe a rapid card technic of blood typing which furnishes a permanent record A drop of type A serum and a drop of type B serum are placed on a card of the type used for filing These drops should be about 5 mm diameter A drop of the patient s blood

(8) J A M A 118 303 J 1 194

or plasma is hastened and intensified when the red cells are suspended in a high salt concentration Agglutination may be inhibited when unheated and stored serum is used although no visible hemolysis is detectable Heating to 55 C alters the serum proteins which in unheated serum inhibit antibody reactions Similarly, higher salt concentrations stabilize the labile globulins and allow flocculation to take place The increased salt concentration intensifies both the strength and the speed of agglutination (see Table) Incubation at 37 C further enhances the effect Equal amounts of the red cell suspension and serum or dilutions of serum in isotonic salt solution are used

EFFECT OF SALT CONCENTRATION ON AGGLUTINATING ACTION OF UNHEATED SERUM (GROUP 0) ON B RED CELLS

SERUM DILUTION	ACTION AT ROOM TEMPERATURE ON RED CELLS SUSPENDED IN					
	0 9% N Cl			3% N Cl		
	At 1 Min	At 15 Min	At 1 Hr	At 2 Min	At 15 Min	At 1 Hr
Undiluted	−	+	+	+++	++++	++++
1 2	−	+	+++	+++	++++	++++
1 4	+	++	+++	++	++++	++++
1 8	−	++	+++	+	++++	++++
1 16	−	+(+)	+++	−	+++	+++
1 32	−	+	+++	−	+	++
1 64	−	±	++	−	−	+
0	−	−	−	−	−	−

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The increased salt concentration however is itself capable of inhibiting agglutination especially in higher serum dilutions Although the speed and strength of agglutination are at first much increased the end titer may be lower

As a suspension medium for red cells a 2 per cent solution is best for use with equal amounts of heated serums when unheated serums are used a 3 per cent solution is more effective although a 2 per cent solution

is generally successful This procedure makes it possible to avoid the false negative reactions caused by inhibition of agglutination or hemolysis which may occur in the examination of unheated serum in blood grouping particularly in cross matching tests

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Fig 54.—P m n t d I t t l m l t sed f blood gr p (Th lh m Myr n)

The authors describe a rapid card technic of blood typing which furnishes a permanent record A drop of type A serum and a drop of type B serum are placed on a card of the type used for filing These drops should be about 5 mm diameter A drop of the patient s blood

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about 2 5 mm diameter is placed next to each drop of typing serum Serum and blood are then mixed thoroughly with a toothpick the mixture being spread to a circle about 1 5 cm in diameter The card is rotated slowly until maximum agglutination has occurred and the drops are then allowed to dry

Blood groupings so determined furnish a permanent record (Fig 54) which can be attached to the history sheet The mixture of blood and serum absorbs slightly into the paper and this film is almost impossible to remove when completely dry

Infusions of Blood and Other Fluids into the General Circulation via Bone Marrow When mercury is injected into the marrow cavity of the sternum or into the tibia and humerus of infants (Fig 55), the metal may be seen by fluoroscopy to escape rapidly through the emissary veins into the general venous circulation It has been demonstrated that micro organisms injected into the bone marrow of guinea pigs may be found in various organs almost immediately after injection These facts indicate the existence of unsuspected anatomic relationships between the bone marrow vessels and the general circulation Advantage has been taken of this knowledge to use the marrow cavity for rapid introduction of blood as well as other fluids into the blood stream Leandro M Tocantins and James F O Neill[7] (Jefferson M College) describe technic and results

TECHNIC —Technic differs slightly depending on the bone selected In the sternum of adults site of election for puncture is either the manubrium or the body of the sternum midway between the angle of Louis and the xiphoid process After preliminary injection of the skin subcutaneous tissue and underlying periosteum with procaine the needle (Fig 58) is inserted vertically with the bevel up and the periosteum is penetrated with a to and fro twisting motion until a good foothold is obtained (Fig 56) Then the needle is tilted until it makes an acute angle of about 30 degrees with the skin surface and with a semicircular to-and fro motion the anterior plate of the sternum is penetrated (Fig 56) A

(7) Surg Gynec & Obst 73 281 87

definite sensation of diminution in bony resistance is felt when the cavity is penetrated Practice on the cadaver enables one to acquire appreciation of this diminution in resistance

Once the marrow cavity is penetrated the ball guard is adjusted and the stylet is removed from the inner needle (Fig 56) A syringe containing about 1 cc saline solution is attached to the needle and gentle aspiration is applied If the needle is properly placed and the marrow is vascular the blood marrow mixture will on aspiration flow into the syringe with little effort (Fig 57) The degree of force required to aspirate the marrow gives some indication of its density Only 0 1 cc or less of marrow should be aspirated The inner needle with the syringe is then removed flushed through with clear saline solution (Fig 57 inset) and reinserted in the outer needle while alternately aspirating and injecting saline solution through it The purpose of this step is to remove air from the lumen of the outer needle At this point 1 2 cc saline solution is slowly injected into the marrow cavity (Fig 57) Immediately afterward the inner needle is removed (Fig 57 inset) and the adapter from the air free saline solution filled rubber tubing and reservoir is attached to the saline solution filled outer needle (Fig 57) Swiftness of manipulation is important to insure against clotting of marrow in the needle



Fig 55 — Film of newborn inf[illegible] marrow injected [illegible] upper end of tibia (arrow) and [illegible]

Penetration of the bone is accompanied by moderate discomfort marrow aspiration elicits a slightly unpleasant drawing sensation injection of saline solution also causes slight discomfort Once these steps have been completed no further discomfort is experienced during the infusion

Usually the flow from the body of the sternum is slow (2 4 cc per minute) at first in 10 to 15 minutes it is accelerated If it is necessary to add material to the

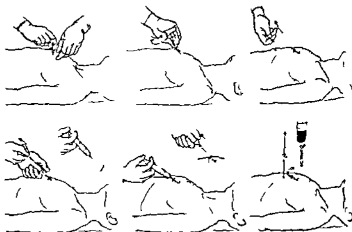
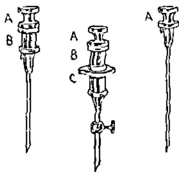


Fig 56 (top) —Tech fo nfus ng ubstan e nto bo e marro f human stern m Left t ight penet at on of skin, subcutaneo s t ue and p r te m ent ng bone and ma r w sem otat ry m t n rem j of t let adjustm nt of guard
Fig 57 (bottom) —Left t ight p ti n of marr w set flu h ng out nt l needl t oduct on f n dl i j ction of al ne t set. remov l f tern l eedl c n e t n to g a ty i f n pt tus.

buret the tube must be clamped below the dropper before bringing the buret down to prevent occlusion of the needle lumen with marrow by reflux pressure In a child under 3 the sternal marrow is not sufficiently developed to allow use of this site In babies or young children the needle should be inserted about 2 3 cm below the proximal end of the tibia or in the femur about the same distance above the external condyle When these sites are used the needle should be pointed toward the diaphysis to avoid injury to the epiphyse i,e

Several precautions should be observed In general no material should be injected unless a blood marrow mixture has been clearly obtained by aspiration Failure of such aspiration may be due to the following (1) The needle may not be in the marrow cavity (2) Rarely the marrow is not sufficiently vascular because of replacement by cellular infiltration fibrous tissue or bone proliferation (3) The distal opening of the needle may be lying against a bone spicule Turning the needle about a semicircle may clear the obstruction When the sternum is used care should be taken not to penetrate the posterior plate Removal of all air from the lumen of the needle is especially important in infants who may not tolerate injection of even a small amount of air



F g 58 —C mpo nt p rt f dl d tyl t AB nt l n il (g ge 18) w th tyl n pl ABC tyl t t l dl a d te l fl (g g l) w th gu l Th d bl 3 5 d 5 m l gth x l d g hub

Fifty two infusions of various fluids including citrated blood plasma 5 per cent glucose and physiologic saline into the bone marrow of 40 patients (33 adults and 7 infants) have been carried out There were no local constitutional immediate or delayed reactions accompanying or following any of the infusions From 50 to 2 000 cc fluid has been infused by gravity at 0 4 25 cc per minute This type of infusion should find its greatest use when rapid absorption of unchanged substances is the chief object and the intravenous route is not available Such may be the case in patients with widespread burns mutilations generalized edema or circulatory collapse and in adults or children who have a poorly developed venous system or whose veins have been ren

dered useless by repeated punctures or by injections of hypertonic solutions it is also useful in emergencies.

This method seems to be contraindicated in generalized infections accompanied by bacteremia the long permanence of the needle in the marrow may encourage localization of a suppurating process at that point No hypertonic or other irritating solutions should be infused through this route because of their possible effect on adjacent marrow and bone

Blood Transfusion Reactions Their Causes and Prevention Leo M Zimmerman Anne Marie Strauss and Harold Laufman[8] (Michael Reese Hosp Chicago) analyze five series of 500 transfusions each tracing the gradual reduction in incidence of transfusion reactions as the various causative factors are successively eliminated Blood transfusion reactions may be classified as (1) pyrogenic or febrile, (2) allergic and (3) hemolytic Pyrogenic reactions are the most frequent These consist essentially of a chill coming on during or shortly after the transfusion followed by a sharp elevation of temperature which returns to normal in 24 to 48 hours A major pyrogenic reaction involves a temperature rise of at least 2 degrees above the pretransfusion level a minor reaction presents temperature elevation of less than 2 degrees Pyrogenic reactions are not followed by jaundice urinary retention or hemoglobinuria which indicate an incompatibility or hemolytic reaction While the pyrogenic reaction is of itself not dangerous the added load it imposes on critically ill patients cannot be disregarded

Pyrogenic reactions are caused almost invariably, by inadvertent injection of foreign protein matter with the blood Such foreign material may be present in any part of the transfusion apparatus particularly in the rubber tubing A frequent source of febrile reaction is the water from which the solutions are made or that which is used for final irrigation of the apparatus If during distillation such fluids are incompletely freed from pyrogens

(8) S g 114 961 9 1 D nbe 1941

febrile reactions will ensue Similar reactions are frequently seen following infusions of saline or glucose solutions which contain protein contaminants

Allergic reactions following blood transfusions are usually manifest as urticaria occasionally as asthma or other visceral disturbances Such reactions are readily controlled by adrenalin and are included therefore with the minor reactions They may be seen when a patient receives blood from the same donor for a second or third time or when the donor has a history of allergy Occasionally such reactions can be traced to blood drawn shortly after the donor has eaten To reduce the incidence of this type of reaction allergic persons should not be taken as blood donors and whenever possible blood should be drawn during the fasting state However allergic symptoms frequently occur following transfusions when neither patient nor donor has been known to have allergic tendencies

Incidence of Reactions Following Transfusions

S ries	P r ni			All G c	H mo- L ti	T
	M j	M	T tal			
I D t (m ltipl y g) 1936	(0%)	14 (2 8%)	39 7 8%)	9 (1 8%)	0	48 (9 6%)
II I d t (pen m thod) 1938	30 (6 0%)	5 (1 0%)	3 (7 0%)	2 (0 4%)	0	37 (7 4%)
III I dir t (ly w m th d) 1939	19 (3 8%)	7 (1 4%)	26 (5 %)	10 (0%)	0	36 (7 %)
IV I d e t (t w m th d) 1940	8 (1 6%)	6 (1 %)	14 (8%)	5 (1 0%)	0	19 (3 8%)
V I d t (F b M y 1941)	3 (0 6)	8 (1 6%	11 %)	4 (0 8%	0	15 (3 0%)

E h ries mpos d f 500 ti t a f n

Hemolytic reactions are rare since the general adoption of careful blood typing and cross matching Such reactions are usually due to incompatibility of the bloods although occasionally overheating or prolonged storage of blood may cause sufficient destruction of red cells to cau olytic reaction Universal donor blood gave

no higher incidence of reactions than did blood of homologous groups Clinical manifestations are severe lumbar pain dyspnea cough chills and varying degrees of collapse followed by jaundice and hemoglobinuria These may lead to complete anuria and death from uremia

Investigation of the incidence of transfusion reactions following successive changes in technic indicates a progressive reduction in reaction incidence with elimination of causative factors The highest incidence of reactions (9 6 per cent) followed transfusions with the multiple syringe method This was but slightly reduced by the open method (7 4 per cent) and the early new method (7 2 per cent) using commercial vacuum bottles with pyrogen free sodium citrate The striking fall in incidence of pyrogenic reactions to 2 8 per cent in series IV is ascribed to institution of a system of adequate record keeping and the use of the pyrogen test (rabbit) to detect the source of contamination from which the pyrogenic reactions arose These measures permitted progressive elimination of the various factors responsible for reaction with gradually diminishing incidence of untoward effects This is reflected well in the last series in which only 2 2 per cent pyrogenic reactions occurred With further improvements in technic even better results are to be anticipated

[The next two articles describe certain hemolytic transfusion reactions especially those resulting despite prop r blood group identification but due to the so called Rh antibodies For other discu sions and articles on this problem the reader is referred to this and the following chapter in the 1941 YEAR BOOK OF GENERAL MEDICINE —Eds]

Hemolytic Reactions Following Transfusions of Blood of the Homologous Group Alexander S Wiener[9] (Jewish Hosp of Brooklyn) presents further observations on the role of the property Rh particularly in 6 cases without demonstrable iso antibodies Ten cases are described in which hemolytic reactions followed transfusions of blood of the same group as that of the patient In two of these cases reactions also occurred following trans

(9) A h P th 3 7 50 August 1941

fusions from universal donors' In four cases irregular iso-antibodies were detected in the patients serums. Three of these serums behaved alike giving agglutination reactions corresponding to the property Rh of Landsteiner and Wiener Moreover the patients in these cases all had Rh negative blood and the incompatible donors Rh positive blood, and the patients serums clumped the cells of the donors of the incompatible blood Accordingly these cases belong in the same category as those previously reported by Wiener and Peters and by Levine i e they are cases in which hemolytic transfusion reactions were caused by individual differences with respect to the property Rh In the fourth case with demonstrable iso antibodies the serum reactions were different from those of the standard Rh serums although there was a correlation between them The reactions given by this serum indicate the existence of more than one sort of agglutinogen Rh in analogy for example to the varieties of agglutinogen A A review of all the cases of intragroup iso-immunization with demonstrable iso antibodies which have been encountered by Wiener to date revealed that in seven the Rh agglutinogen was involved in two the agglutinogen A_1 and in one the agglutinogen P

In six of the cases in which hemolytic transfusion reactions occurred no iso antibodies were demonstrable in the patients serum even by the centrifuge technic at refrigerator room and body temperature In view of the findings in cases in which iso antibodies were demonstrable it seemed plausible that in most of these six cases also the hemolytic reactions would prove to be due to iso immunization to factor Rh That this surmise was correct was indicated by the fact that the blood of all six patients was Rh negative while only one of every seven persons taken at random has blood free from this factor Moreover in two patients deliberate transfusion of Rh negative blood was followed by no untoward reaction while transfusions from unselected donors (presumably with Rh positive blood) of the same group as

the patient resulted in hemolytic transfusion reactions

The 10 cases described herein fall into two categories In one group of cases the patients were given repeated transfusions the earlier transfusions serving to immunize them against the Rh antigen and the later transfusions giving rise to the hemolytic reactions In the other group the patients had hemolytic reactions following their first transfusions In every case of the latter group the reaction occurred in an intrapartum or postpartum patient the source of the antigen that immunized the patient having been the fetus in utero It is advocated therefore that in such instances whenever possible Rh negative blood of the same group as that of the patient should be used for transfusion In general a 'safe universal donor would be a person of group O with Rh negative blood and only low titered iso-agglutinins A and B in his serum

These observations explain the erratic clinical results sometimes observed when treating diseases (particularly blood dyscrasias) in cases in which repeated blood transfusions are required Careful selection of compatible blood donors in such instances with special attention to the Rh factor may give better clinical results

Hemolytic Transfusion Reactions Alexander S Wiener[1] (Jewish Hosp of Brooklyn) describes matching tests for detecting intragroup incompatibility and four cases illustrating the application of these tests In three cases iso immunization as a result of previous blood transfusions was detected by the tests the factors responsible being Rh P and M respectively In this way the transfusion of incompatible blood though of the same group as the patient was avoided In the fourth case a hitherto undescribed rare agglutinogen was detected in the patient s red cells through the chance presence in the prospective donor s serum of the corresponding rare iso-agglutinin

The factor most often involved in the rare cases of intragroup transfusion hemolysis is the agglutinogen Rh

(1) Am J Cl n P th 1 20 3 1 June 19 4

In all su h cases therefore the Rh reaction of the bloods of patient and donor should be determined Since iso immunization against factors M and P can occur in man though this phenomenon is rare the question arises why hemolytic tran fusion reactions ascribable to these fac tors have not been reported Such cases are probably very rare because M and P are very poor antigens in man and possibly in addition when such cases were encountered previously they were not recognized because when incompatibility was detected in the slide test the donor was simply rejected and the issue was not pur sued

The slide technic of cross matching usually fails to detect incompatibility due to the Rh factor Therefore in pregnant women and patients receiving repeated transfusions it is necessary to carry out the direct match ing test in test tubes recommended by Levine

TECHNIC —Two drops of the patient s blood is mixed with a drop of the donor's cell suspension in a small test tube incubated at 37 C for 30 minutes and centrifuged at low speed for 1 minute The tube i then *gently* shaken and in spected for evidence of agglutination Since in some cases the agglutinins are most active at low temperature tests should be set up simultaneously at room and refrigerator tem peratures (Wiener and Peters) To rule out auto agglutina tion most apt to occur at low temperatures a control test should be made using a mixture of the patient s serum and own blood cells Auto-agglutination can also be prevented by eparating the patient s erum or plasma from the cells at low temperature and by using for the actual tests blood cell suspensions washed once with warm (body temperature) saline solution

A problem of some importance is the relation of auto agglutinins to hemolytic transfusion reactions In Wiener s experience auto agglutinins at least those of the common type which act best at low temperatures and not at body temperatures are not responsible for such reactions In this connection there are reports of three cases of acute hemolytic anemia following sulfonamide drug therapy Although all three patients had strong serum auto a glutinins they responded satisfactorily to

blood transfusions In patients having auto-agglutinins in the serum Wiener performs a biologic test before giving a transfusion since it is possible that the autoagglutinins may obscure some iso antibody capable of causing a hemolytic reaction

[The reader should consult the original article for further details — Eds]

HEMOLYTIC ANEMIAS

Included in this section are articles dealing with various types of hemolytic anemias which may be classified as to etiology to a certain extent h moly is by drugs (sulfonamides phenylhydrazine) hemolysis from stagnation of blood in the spleen (familial jaundice hyperemic splenomegaly) or other tissues (erythroblastosis foetalis sicklemia) hemolysins demonstrable in vitro (autohemolysinic anemia) In other articles, the effects of splenectomy are discussed —Eds

Acute Hemolytic Anemia Developing during Therapy with Substances Belonging to the Sulfanilamide Group Basing his observations on a study of 90 cases, Mogens Trier (Blegdams Hosp Copenhagen) discusses the predisposing factors and the clinical picture of the acute hemolytic anemias arising during sulfonamide therapy Anemia arising during treatment with sulfanilamide seems to be more frequent in children (8 9 per cent) than in adults (1 3 per cent) Sulfathiazole therapy on the other hand elicits hemolytic anemia much less frequently in either age group and when such anemia does occur it is usually in adults Sex is apparently of no consequence There is no apparent correlation between dosage or blood level of the sulfonamide nor does the acuteness or chronicity of the infection have a role in the development of hemolytic anemia A rise in temperature during treatment has been postulated as having etiologic significance

Hemolysis occurs suddenly usually during the second to fifth day of treatment although it has been reported as late as 11 and 20 days after institution of treatment Prodromal symptoms in the form of other toxic reactions

( ) Acta med Scand n 108 117 131 1

often occur during the first two days of treatment fre quently there are pronounced nausea and vertigo and conspicuous exhaustion With the occurrence of hemoly sis a secondary rise in temperature is characteristic The affection per se is characterized by a sudden fall in hemoglobin and erythrocyte values jaundice urobili nuria leukocytosis and reticulocytosis and in more severe cases by hemoglobinuria hemoglobinemia and hepatomegaly

Pathogenesis is obscure and is probably due to indi vidual idiosyncrasy Prognosis is good Treatment con sists of withdrawing the drug and facilitating its excre tion by oral administration of large amounts of water Transfusion may be necessary

[It has been shown that *at the onset* the hypotonic fragility of the red blood cells may be greatly increased Note also that phenyl hydrazine anemia is associated with such increases in fragility as stated in a later article —Eds]

Acute Hemolytic Anemia from the Sulfonamides The acute hemolytic anemia of sulfanilamide and sulfa pyridine therapy was studied in four cases two of them fatal by Charles L Fox Jr and Reuben Otten berg[3] (Columbia Univ) Spectrophotometric analysis revealed that the red cells that survived hemolysis were essentially normal containing little methemoglobin or sulfhemoglobin The serum 12 48 hours after onset of hemolysis contained 0 4 1 7 Gm per cent of three blood pigments hemoglobin methemoglobin and contrary to expectation not sulfhemoglobin but Fairley s new pig ment methemalbumin No evidence was found for in volvement of methemalbumin in the hemolytic process it was not excreted in the urine

Occurrence of large proportions of methemoglobin in the serum with less in the intact red blood cells suggests the possibility that it was the red blood cells containing methemoglobin which underwent hemolysis This might indicate that formation of methemoglobin in the red blood cells was an etiologic factor As methemoglobin is formed from hemoglobin only by oxidizing agents the

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(*) Acta med Scand v 109 117131 194-

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uniform occurrence of some methemoglobin in the red cells of all patients treated with the sulfonamide drugs is excellent evidence that the body produces oxidizing agents from these drugs Furthermore, one such oxidant hydroxylaminobenzene sulfonamide, can penetrate the erythrocyte membrane and is detectable in the urine during sulfanilamide therapy The contrast between the frequency of methemoglobin in the red blood cells and the infrequency of hemolytic anemia shows that, although oxidizing agents are usually formed, they per se are not hemolytic Furthermore if the usual oxidation products were hemolytic, one would of necessity expect hemolysis to parallel methemoglobin formation This is not the case Most patients receiving huge doses over long periods with correspondingly large amounts of methemoglobin in their cells do not develop hemolysis On the other hand when hemolytic anemia occurs it appears early—within two to five days from the start of therapy and after only moderate doses of the drug Accordingly certain individuals may form unusual oxidation products which are hemolytic and which are present in or affect chiefly the red cells containing methemoglobin For example the nitro compound representing a further stage of oxidation of the amino group of sulfanilamide than the hydroxylamine is more toxic as well as more bacteriostatic [Ham and his associates have shown that certain oxidants are capable of causing striking increases in hypotonic fragility of red blood cells in vitro and in experimental animals —Eds] Presumably, this peculiarity is permanent for the individual for in three of four patients who once suffered acute hemolytic anemia from sulfanilamide readministration of the drug a year later again induced this syndrome and on the identical day

Approximate calculations were made of the amounts of hemoglobin liberated in these explosive hemoglobinemias Comparison with the small amounts left in the circulation after 12 to 48 hours and the still smaller amounts (4 per cent or less) excreted ... neys

shows that the body has means of removing rapidly from the plasma some 500 700 Gm hemoglobin without the aid of renal excretion

Shock was a prominent symptom most marked in the fatal cases The hemolyzed cells in these cases represented about 30 per cent of the total blood volume This great reduction in blood volume following the demonstrated rapid removal of the products of hemolysis from the circulation may be a factor in the explanation of hemolytic shock In the severest cases transfusion was of no great benefit possibly because of further hemolysis of the new blood Plasma transfusion would be free of this danger

Familial Acholuric Jaundice Associated with Bone Changes Eric L Cooper[5] (Melbourne) reports on a family presenting acholuric jaundice or hemolytic splenomegaly of the Chauffard Minkowski type The mongoloid facies described by Cooley in erythroblastic anemia and also the changes in the skull bones reported in sickle cell anemia and erythroblastic anemia were present

Progressive growth of bone marrow in the membranous bones of the cranial vault in acholuric jaundice leads to an enormous increase in the thickness of the diploe The diploe extends to the outer surface of the bone and the bony trabeculae of the diploe appear as relatively regular lines of bone formation arranged at right angles to the surface of the inner table of bone This radial arrangement of the bony trabeculae follows the deposition of bone by the mesenchymal cells of the membrane which is giving rise to the parietal and frontal bones Hyperplastic red bone marrow largely replaces the osteoblastic tissues and a greater proportion of the thickness of the skull consists of masses of marrow separated by fine strands of bone

Ground sections of the parietal bone (Fig 59) show well the contrast between the deeper layers of the diploe and the newly formed superficial bone and roentgenograms of these bone sections (Fig 60) show the radial

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appearance of the superficial layers of bone During life roentgenograms of the skull show a similar appearance which has been described by Sear as "hairs growing from the inner table"

Microscopically the bone of these vertical trabeculae shows irregular laminations and irregular ossification in



Fig 59—Gr u d se t on of f ontal b ne shows d nse inter al bo e a d p us b th oughout rema nder of thickne s

the fibrous tissues Active erythropoietic marrow tissue is everywhere in close contact with the bony trabeculae There is complete absence of any fat cells in the bone In some areas the marrow shows degenerative changes

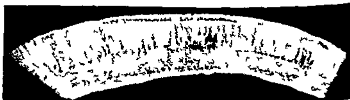


Fig 60—Ro ntgen pp a of gr und sect n of bo e 0 5 mm thi k sh w d nse nt r l l m d ary diploe a d new b ne laid down in erti l lu s

and it may also at times be partly replaced by dense scar tissue

The evidence suggests two distinct processes in the bone active hyperplasia of bone marrow and formation of new bone and an exhaustion of the overstimulated marrow and replacement of the degenerating cells by fibrous tissue

[The occasional a ociation of congenital hemolytic jaundice and tower skull should be recalled in this connection —Ed]

Hyperemic Splenomegaly, Intensified Hemolysis Increase of Fibrinogen and Accelerated Sedimentation of Red Cells E Fagerberg S E Fagerberg and R Fåhraeus[6] (Univ of Uppsala) state that in general the sedimentation rate of the red cells gives an approximate indication of the fibrinogen concentration of the plasma Fibrinogen derives from the cellular elements of the blood particularly from the red cells as shown by experiments of Reymann and Davide This is confirmed by the authors studies on rabbits they found that intravenous injection of distilled water (40 cc) lysolecithin (100 mg) and red cells from another rabbit (30 cc) increases the plasma fibrinogen proportionately to the hemolysis in addition they observed that ligation of the pancreatic duct which is known to increase considerably the fibrinogen content of the plasma produces also a decrease in the number of red cells Consequently there is an intimate relation between artificial destruction of red cells and increase of plasma fibrinogen

[This thesis neglects entirely the much more plausible evidence that fibrinogen is formed in the liver —Eds]

The question of spontaneous destruction of red cells is clarified by recent studies on the physiology of the spleen Knisely has demonstrated that the essential result of the reservoir function of the organ is the separation of the red cells from the plasma by filtration in the venous sinuses Pergenhem and Fahraeus have shown that one of the consequences of this separation is the preparation of the red cells for hemolysis and Mellgren has found that the blood of the splenic vein deriving from the spleen while it fulfil its reservoir function is spontaneously hemolyzed mostly in the liver The intensity of the hemolyzing function of the spleen runs parallel to its reservoir function and the increase in the latter can be estimated only by enlargement of the organ caused solely by circulatory congestion

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During pregnancy of women rabbits and guinea pigs the spleen is considerably enlarged by hyperemia, which is undoubtedly the expression of an increase in its reservoir function Pregnant women show signs of increased destruction of red cells (bilirubinemia reticulocytosis) and anemia is so common among them that Gram has called it physiologic anemia of pregnancy They present an increase in plasma fibrinogen and in the sedimentation rate of the red cells which reaches 40 mm per hour about the time of labor

Similar changes occur during the first week in the new born The spleen is enlarged from the second to the fifth day after birth and during this time the number of red cells decreases notably The rapid destruction of the red cells is regarded as one of the causes of icterus of the new born The plasma fibrinogen and the sedimentation rate which are minimal at birth rise rapidly during the first week of extra uterine life

In infectious diseases hypertrophy of the spleen is nearly constant and is due to hyperemia, according to Grober Jakobs Ziegler and Kaufmann This can only mean an increase in the normal reservoir function of the spleen and a consequent destruction of red cells In fact the number of red cells is decreased in most infections and the decrease is proportionate to the length of the disease The hemolytic action of the spleen is probably intensified by the high temperature of the body as Fahraeus has found that the alteration of the red cells and of the plasma when they are kept apart, is much greater at 40 C than at 37 C and that this is particularly apparent in the red cells There is nearly always an increase in the plasma fibrinogen and consequently in the sedimentation rate of the red cells An important exception to this rule is the small group of infectious diseases previously known as pyrexias the best representative of which is typhoid Splenomegaly is a factor in the clinical diagnosis of this disease But the number of red cells remains normal and the fibr[illegible] content of the plasma is normal or even below[illegible] The ex

planation lies in the fact that clinicians have always stressed the greater hardness of the spleen in typhoid than in other infectious diseases and that pathologists state that the changes in the spleen of typhoid present the characters of productive inflammation The splenomegaly would therefore be due to an increase in the fixed elements of the organ and not to circulatory congestion The increase in the sedimentation rate is caused by an increase in the serum globulin of the plasma

Consequently there is a cause and effect relationship between hyperemic splenomegaly intensified hemolysis increase in plasma fibrinogen and accelerated sedimentation rate of the red cells

Primary Splenic Neutropenia Newly Recognized Syndrome Closely Related to Congenital Hemolytic Icterus and Essential Thrombocytopenic Purpura is described by B K Wiseman and Charles A Doan (Columbus O) The essential condition in five cases was profound granulopenia panhyperplasia of the marrow and splenomegaly with recovery after splenectomy Varying degrees and combinations of hemolytic anemia and thrombocytopenic purpura were encountered and coincidentally corrected In each case the anemia was hemolytic with elevated reticulocyte count and icterus with negative direct van den Bergh reaction Case 1 showed principally neutropenia but also definite thrombocytopenia and hemolytic anemia Case 2 although exhibiting chiefly neutropenia on first observation two months later showed not only more profound neutropenia but also hemolytic anemia and severe thrombocytopenia Case 3 showed the most extreme and pure example of neutropenic leukopenia at no time was there hemolytic anemia but some nonsymptomatic thrombocytopenia developed by the time of second admission Case 4 presented thrombocytopenic purpura as the most striking feature probably present as a secondary manifestation of primary splenomegalic neutropenia Case 5 showed

(7) Ann I t Med 16 1097 1117 Jun 1942

obtained by washing the cells with saline at 50 C The patient was found to be a group A subgroup A type MN whose serum contained auto agglutinins and also anti O and anti A agglutinins presumably the result of a previous transfusion from a universal donor and a group A donor It was impossible to separate the auto agglutinins from the red cells by centrifuging washing resuspending in saline and heating to body temperature The intensity of agglutination thwarted efforts to demonstrate the presence of auto hemolysin, although there seemed to be some hemolysis following incubation overnight It was thought that in addition to the auto agglutinin and anti O and anti A agglutinins, there might also *be Rh antibodies but these could not be demonstrated*

After transfusion with group A, type M blood the patient had a severe chill followed by temperature rise to 105 8 F Rise in hemoglobin and erythrocyte levels was only transient and the patient was more deeply jaundiced and his blood showed no trace of the M cell A second transfusion was followed by a similar reaction There was no hemoglobinuria following either transfusion

To remove the chief site of blood destruction splenectomy and liver biopsy were performed Plasma (250 cc type A) was given during the operation Postoperative erythrocyte count was 550 000 (15 per cent hemoglobin) the next day it was 880 000 (2_ per cent hemoglobin)

The spleen weighed 400 Gm Microscopic section showed great congestion of the pulp, with numerous islands of extra medullary hemopoiesis The liver section showed normal hepatic architecture with islands of extramedullary hemopoiesis and periportal infiltration of round cells and occasional eosinophils

Postoperative course was uneventful until the third day, when pneumococcic pneumonia developed Sodium sulfapyridine given intravenously caused prompt fall in temperature and striking improvement within 12 hours On the fourth postoperative day the auto agglutinin titer was still high but it was decided to hazard a transfusion Five hundred cc *group A blood diluted with saline was given in fractionated* amounts without reaction The red cell count rose to 1 250 000 with 34 per cent hemoglobin and many normoblasts appeared A second transfusion was similarly given without reaction, and the red cell count rose to 2 1_0 000 with 48 per cent hemoglobin indicating that blood destruction had practically ceased The auto-agglutinins persisted despite absence of reaction There were 1_1 normoblasts per 100 white cells and this was reflected in the Price-Jones curve which showed a falling off of the number of microcytes in macrocytes On the seventh postoperativ

ture rose and the patient experienced abdominal pain and passed large amounts of chocolate-colored blood by rectum The red cell count fell to 1,130 000 with 26 per cent hemoglobin. Hemorrhage continued and he died the ninth postoperative day

In this case the auto-antibodies caused destruction of blood cells introduced from without as long as the spleen was present but following splenectomy transfusions were tolerated with rise in the blood count despite the presence of the auto-antibodies

[It is interesting that although strong auto-agglutination was present autohemolysins were not demonstrated in vitro in this patient. If auto-agglutination occurs in vivo it may be assumed to cause hemolysis from resulting stagnation of the blood as already suggested by Ham and his associates and by Fåhraeus and his associates (this YEAR BOOK p 37 —Eds.]

Role of Iso Immunization in Pathogenesis of Erythroblastosis Foetalis Philip Levine Lyman Burnham E M Katzin (Newark, N J Beth Israel Hosp) and Peter Vogel[9] (Woman's Hosp New York City) present data which indicate that erythroblastosis foetalis results from (1) iso-immunization of the mother by dominant hereditary blood factors in the fetus as evidenced by the production of immune intragroup agglutinins and (2) the subsequent passage of these maternal agglutinins through the placenta and their continuous action on the susceptible fetal blood In most cases (93 per cent) the blood factor involved has been shown to be *either identical with or related to the Rh (rhesus) agglutinogen* first described by Landsteiner and Wiener with the aid of rabbit serums prepared by injection of rhesus blood In other words the rabbit anti rhesus immune serums and the serums of pregnant women experiencing intragroup transfusion accidents gave almost identical agglutination reactions on all human bloods tested Accordingly a pregnant woman whose blood does not contain the Rh factor (Rh negative occurring in about 15 per cent of the general population) if married to an Rh husband (85 per cent in the random population) may produce anti Rh *agglutinins as a result of immunization*

(9) Am J Obst & Gynec 4 9 936 December 1941

with the Rh fetal blood Should these agglutinins penetrate the placenta in suitable concentration they may serve as the source of the intra uterine hemolysis of fetal blood the characteristic feature of erythroblastosis foetalis

The hereditary nature of erythroblastosis foetalis, hitherto unknown, can now be stated in terms of the iso-immunization theory In some families every pregnancy but perhaps the first terminates in an abortion a still birth or an infant with erythroblastosis foetalis in other families only one of several pregnancies results in an affected infant Since the Rh factor is inherited as a simple mendelian dominant it is obvious from a genetic standpoint that this striking difference in familial incidence of the disease is determined by the homozygosity (RhRh) or heterozygosity (Rhrh) of the father's blood. The first born is frequently (but not always) spared because more than one pregnancy with an Rh positive fetus may be required before a sufficient degree of iso-immunization is attained

Javert has stated that erythroblastosis foetalis in one of its several forms occurs once in 400 deliveries but this condition probably has a still higher incidence especially if some cases of habitual abortion and stillbirths are manifestations of iso-immunization Actually the incidence of matings in which iso-immunization with Rh may occur (Rh positive husband and Rh negative wife) is 85 by 15 or 13 per cent of all matings Consequently a much higher incidence of erythroblastosis foetalis would be expected However certain factors tend to reduce this incidence such as the current tendency to small families and the inability of many Rh negative women to respond to iso-immunization

The data on erythroblastosis foetalis and the recent studies on iso immunization with the blood factors A and B in the absence of any pathologic conditions in the mother or the infant indicate that immunizing substances derived from the fetus make their way through the placental barrier into the maternal circ[illegible] nce the

Rh factor in contrast to the A and B substances is probably limited to red blood cells it is assumed that fetal blood in one form or another penetrates the villus in sufficient quantity to induce immunization in the mother

Agglutination tests for the Rh factor are valuable in laboratory diagnosis of erythroblastosis foetalis Intra group transfusion accidents associated with pregnancy can now be prevented by use of Rh negative donors and by use of modified cross matching test

[For technic ee art le by Wiene this YEAR B OK p 0 — Eds]

Symptomatic Hemolytic Anemia may be defined as a hemolytic syndrome often indistinguishable by hemato logic methods from familial hemolytic jaundice but showing a definite etiologic relationship to such under lying diseases as neoplasm (teratoma sarcoma) leu kemia and Hodgkin s disease Frequently but not regu larly the pathologic lesions are situated in the spleen thu suggesting a splenic disorder That the hemolytic process in these cases is not merely coincidental is demonstrated at least in some instances by the dis appearance of all signs of the hemolytic process fol lowing successful treatment of the accompanying disorder Thus removal of a dermoid cyst may result in complete cure of severe hemolytic anemia Karl Singer and William Dameshek (Boston) present cases demonstrating this relationship One is given here

Woman 47 admitted May 8 1939 complained of increas ing pallor weakne s and dyspnea since the first of the year Examination showed marked pallor and slight jaundice There were arteriosclerotic chan es of the retinal ves els a rough blowing systolic murmur in aortic area and hyperten sion (198/108) The edges of both spleen and liver were ju t palpable A mass the size of an orange wa felt in the region of the left ovary

Blood studies showed hemoglobin 34 per cent re l cells 1,500 000 white cells 10 800 platelets 646 000 marked spherocytosis 46 per cent reticulocytes Three metamyelocytes and 2 myelocytes were noted in counting 100 white cells Mean cell volume was 78 cu microns mean cell diameter 6

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microns and mean cell thickness 2 8 microns Hemolysis in hypotonic sodium chloride solutions began at 0 68 per cent and was complete at 0 4 per cent Singer's lysolecithin fragility test was normal Urine contained no bile, but increased urobilinogen was demonstrated Serum bilirubin (indirect) measured 5 mg per cent

On the basis of spherocytosis and increased hypotonic fragility, diagnosis of congenital or familial hemolytic jaundice was at first made despite the rather atypical and relatively acute onset and complete absence of familial hemolytic disease Normal lysolecithin fragility was also against the familial type of disease Splenectomy was advised

June 28 the anemia was somewhat greater and nucleated red cells were common (5 7 per 100 white blood cells) Spleen and liver extended 2 fingerbreadths below the costal margins After transfusion of 500 cc blood splenectomy was performed on July 6 A second transfusion was given postoperatively Atelectasis of the left lower lung occurred the next day A third transfusion was given July 23 because the hematologic response was unexpectedly slow

By September 6 the red cell count had reached 4,190 000 hemoglobin 77 per cent, and there had been striking drops in reticulocytes (4 5 per cent) and bilirubin content of the blood (to 0 9 mg per cent) However in October the patient again began to feel poorly Examination on November 24 showed jaundice of the scleras and skin and greatly enlarged liver now palpable 4 fingerbreadths below the right costal margin. Red cell count had dropped to 1 240 000 and hemoglobin to 24 per cent Various procedures such as intravenous injection of congo red abdominal irradiation use of large do es of liver extract and iron were ineffectual No accessory spleen was demonstrable by roentgenograms The course was steadily downhill, interrupted only by repeated blood transfusions 24 of which each of 500 cc, were given from November 24 to February 29 1940 with only transient rises in hemoglobin and erythrocyte counts It was then decided to institute active search for an accessory spleen or a dermoid cyst of the ovary Exploratory laparotomy on February 29 revealed no accessory spleen but a large round mass arising from the left ovary was discovered and removed with the accompanying tube Biopsy of the liver was also performed

Following this operation the hemolytic process gradually subsided and in about four months the hematologic picture was normal Spherocytosis and increased fragility of erythrocytes disappeared completely, coincidentally with an increase in mean cell diameter from about 6 to 7.35 microns Serum bilirubin dropped to normal Urobilinogen the

fece (9 000 mg daily in December) fell to 86 mg daily
The thick walled unilocular dermoid cyst measured 7 cm in diameter it contained no definite splenic tissue Liver biopsy showed infiltration of the portal spaces by numerous lymphocytes definite proliferation of the bile ducts and areas in the sinusoids containing many polymorphonuclear leukocytes The most marked change was the increased prominence of the Kupffer cells which were filled with hemosiderin

This appears to be an example of symptomatic hemolytic anemia which was temporarily improved by splenectomy but in which cure was obtained only after removal of a dermoid cyst However the coexistence of a dermoid cyst and hemolytic anemia does not necessarily indicate an etiologic relationship This is illustrated by a case of Watson s in a 19 year old girl in whom hemolytic anemia and a large ovarian cyst were associated Marked auto-agglutination of red cells was observed Oophorectomy had no effect but splenectomy led to slow steady improvement and complete recovery This observation indicates that a dermoid cyst is not necessarily the entire cause of a hemolytic process but that it might have a definite relationship It is possible that these patients may require removal of both the tumor and the spleen

The authors present additional histories of cases of hemolytic anemia associated with Hodgkin s disease leukemia hepatic and infectious diseases Diagnosis of symptomatic hemolytic anemia may be difficult Diagnosis of the hemolytic component should at least be suspected from presence of jaundice with pallor and absence of bile from the urine The spleen is palpable in most cases Further study will reveal bilirubinemia with an indirect van den Bergh reaction normal or dark colored feces with greatly increased urobilinogen output and usually an increase in urinary urobilinogen Spherocytosis should be recognizable in most cases All the evidences of increased regenerative activity of the bone marrow are also present The bone marrow shows extreme hyperplasia particularly of the erythroblastic elements Prognosis depends on the underlying disease

Present Status of Surgery of the Spleen is discussed by John deJ Pemberton[3] (Mayo Clinic) Aside from the disease for which splenectomy is undertaken the operative difficulties and the condition of the patient as affected by associated diseases there are two important factors which influence the operative hazard the presence of hepatic impairment and patient's age Mortality rises steadily in patients over 40 Hepatic damage concurrent with splenomegaly is found most frequently in splenic anemia but occasionally it may be found in cases of hemolytic icterus of long standing Another hazard associated with splenectomy is the development of postoperative portal or mesenteric thrombosis This complication is usually limited to cases of splenic anemia and infectious splenomegaly but accounts for most of the mortality in such cases

Indications for splenectomy have become better defined It is now contraindicated for some conditions in which it was formerly advocated Thus pernicious anemia is no longer an indication for splenectomy Likewise splenectomy offers little or no benefits for septic splenomegaly myelogenous leukemia lymphoblastoma and polycythemia vera

Splenectomy is the treatment of choice in all cases of hemolytic icterus for the operation is attended by only nominal risk and is practically curative Benefits become apparent early as shown by rapid improvement in the anemia and fading of the jaundice However certain blood changes such as microcytosis and increased erythrocyte fragility commonly persist throughout life

In mild or moderate hemorrhagic purpura splenectomy is not recommended until medical measures have failed In the acute forms since the dangers of neglect far outweigh those of operation and since splenectomy is the most certain means of causing a remission of the bleeding tendency commonly complete and permanent splenectomy is indicated in each case as soon as possible

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after the diagnosis has been definitely established

Splenectomy in cases of splenic anemia or Banti's syndrome lightens the load that has been thrown on the liver by reducing the volume of blood entering the portal circulation, removes possible toxic substances originating in the spleen, removes the splenic factor in blood destruction and produces adhesions for the establishment of collateral circulation. Results are gratifying even in many cases of advanced splenic anemia with hepatic damage. Rapid improvement in the anemia and a rise in the leukocyte count are followed by general improvement of health. Because hemorrhage from gastric or esophageal varices persist in many of these cases even after splenectomy, omentopexy is advocated as a supplementary procedure in such cases.

Hematologic Changes Following Splenectomy in Man, with Particular Reference to Target Cells, Hemolytic Index and Lysolecithin. Karl Singer, Edward B. Miller and William Dameshek[4] (Boston) conducted a hematologic study on 19 patients in whom splenectomy had been performed from 4 weeks to 15 years previously. Howell-Jolly bodies in erythrocytes were a constant finding after splenectomy and target cells—abnormally thin red cells—were usually present. The presence of the latter together with a tendency to thinness on the part of the whole red cell population adequately accounts for the increased hypotonic resistance usually seen and is confirmatory of previous work indicating that the spleen makes red cells thicker and more fragile to hypotonic salt solutions.

A lowered urobilinogen output in the feces was commonly found after splenectomy, indicating a diminution in hemoglobin destruction, perhaps related to increased thinness of red cells. That the urobilinogen output in the feces may be diminished after splenectomy has occasionally been observed in previous investigations. In most recorded human cases diminished output after splenectomy was studied in patients with hemolytic

(4) Am J M Sc 0 171 1 6 A g (1941

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for the postsplenectomized state as this finding is present to some extent in other conditions as in iron deficiency anemia polycythemia hypothyroidism etc In these conditions however the lowered hemolytic index can probably be interpreted as denoting an imbalance between erythrocyte formation and destruction

Lysolecithin metabolism studies in these cases revealed two disturbances i e a frequent lack of increase in lysolecithin in the serum on incubation and a low absolute value of lysolecithin in the peripheral blood Thus splenectomy frequently leads to a disturbance of the whole mechanism of lysolecithin production

Leukocytosis and thrombocytosis were commonly present These findings together with the appearance of Howell-Jolly bodies (inadequate denucleation?) suggest that splenectomy may result in removal of certain normal inhibitory mechanisms of the spleen on the bone marrow [or removal of a filtration mechanism in the spleen—which?—Eds]

These observations indicate that the spleen has a direct effect on the red cells which traverse its sinusoids and an indirect effect on the hemopoietic cells of the bone marrow

Erythroblastic Anemia Following Splenectomy in Cases of Chronic Familial Hemolytic Anemia Erythroblastic response to splenectomy is well known in Mediterranean (Cooley s) anemia In the case of Wollstein and Kreidel *the erythroblastosis was observed until* death which occurred five years after splenectomy The proportion of erythroblasts was as high as 1 435 to 100 white cells while in a case reported by Cooley the highest ratio was 2 200 100 Even the white cell count (disregarding nucleated red cells) is high in these cases Whipple and Bradford reported as the highest *counts 105 600* white and *222 000 nucleated red cells per* cu mm blood In Cooley s case the highest counts were 21 500 white cells and 163 900 nucleated red cells

Although splenectomy is claimed to be the best treatment for chronic hemolytic anemia uniformly good

anemia in whom prior to splenectomy there is a greatly increased blood destruction In the cases presented herein normal indexes after splenectomy were present in a case of Gaucher s disease and in two cases of congenital hemolytic jaundice (where the normal index may indeed indicate slightly increased hemolysis for a splenectomized patient) In all the other cases there was a low hemolytic index with two possible exceptions Of interest was the fact that in two of the four cases of congenital hemolytic jaundice there was despite the continued presence of spherocytosis, a low hemolytic index From these observations alone it would appear that spherocytes despite their abnormal fragility to hypotonic saline are no more readily destroyed than normal erythrocytes [after splenectomy —Eds] The urobilinogen excretion in the feces is the end result of a complicated process and therefore it cannot be concluded that urobilinogen excretion is a direct measure of hemoglobin destruction Theoretically the low hemolytic index found after splenectomy could be due to various causes (1) diminished blood destruction (2) a disturbance in the ability of the body to form bilirubin from liberated hemoglobin and (3) an increased storage of pigment The first possibility namely a reduction in the breakdown of hemoglobin, is the most likely The question arises whether the formation of target cells which are more resistant toward hypotonic saline may be directly correlated with the lowered hemolytic index No direct parallelism was however demonstrable between the actual number of target cells and the degree of the diminution in urobilinogen output A general diminution in thickness not directly measurable may be of greater importance in this connection than the finding of large numbers of target cells It should be noted that target cells are present in considerable numbers in sickle cell anemia and in Cooley s anemia conditions associated with a greatly increased hemoglobin destruction Furthermore a low hemolytic [illegible] cific

The mother blood showed extreme anisocyto is An only brother age 2 had light anemia and extreme anisocytosis and erythroblastosis (hemolytic anemia) The patient was pale with subicteric tinge ot scleras and kin The spleen was greatly enlarged

Test for erythrocyte fragility howe l incomplete hemoly i with a concentration of 0 40 per cent (control 0 40 per cent) and complete hemoly is with a concentration ot 0 28 per cent (control 0 30 per cent) Examinations ot peripheral blood reveale l hemoglobin 8 5 Gm per cent red cell 3 010 000 white cell 8 050 platelets 154 0 reticulocytes 4 01 per cent mean corpuscular volume 93 cubic microns mean corpuscular hemoglobin concentration 31 4 per cent icteric index 24 unit and ratio of nucleated re l cells to white cell 40 100

Nineteen days after admi sion plenectomy was performed Two and a half months after di charge she wa pale and lightly jaundiced and pallor and the light jaundi e per iste l Four months after operation the ratio of nucleated red cells to white cells wa 4 800 200

[The authors do not use th term l me fam lial hemolyt anemia in the usual s n e of the onlt n characterize l by spherocytosis and increased hypotoni frag lity of the erythrocyte So far as can be ascertaine l the fi t ca e wa oi ot a quir d hemolytic anemia (mala a f) an l the other two resemble l Cooley s erythroblast c anemia The article erves to emphas e that splen ectomy is *not* neces arily suc e sful in atyp cal hemolytic anemi s —Eds]

PERNICIOUS ANEMIA AND RELATED MACROCYTIC ANEMIAS

The following articles describe various aspects of such anem as with reference to clinical asp cts etiology and treatment —E l

Primary Hypochromic Anemia Terminating in Pernicious Anemia is described in two cases reported by Edward B Miller and William Dameshek (Boston) one of which is given here

Woman 40 was admitted Jan 17 1933 becau e ot weak ne and anemia Hi tory included transitory dysphagia di like for meat premature grayness brittle finger nail diarrhea glossitis paresthe ias of the fingers and hand palpita tion ankle edema and exertional dy pnea The kin was pal but not icteric The tongue was devoid of coat and papillae and extremely shiny it was definitely atrophied

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results have not been obtained [except in the classic hereditary variety with spherocytosis and increased fragility—Eds.] Eugene Stransky and Arsenio C Regala (Univ of the Philippines) report three cases

CASE 1—Farmer, 23, had had frequent chill fever and sweating for five years Most important findings were light jaundice and enlarged spleen Peripheral blood showed red cells 2 198 000 hemoglobin 45 per cent leukocytes 6 [illegible], color index 1 09 neutrophils 58 per cent lymphocytes 22 per ce[nt] monocytes 2 per cent transitional cells 2 per cent, eosinophils 13 per cent basophils 1 67 per cent premyelocytes 0.3[illegible] per cent staff forms 1 per cent, reticulocytes 2 2 per cent platelets 358,000, cell volume 21 per cent volume index 1 19 mean corpuscular volume 100 cubic microns mean corpuscular hemoglobin 29 5 micromicrograms and mean corpuscular hemoglobin concentration 29 5 per cent

Four days after splenectomy the red cell count was 1 [illegible] 000 nucleated cell count (red and white cell) 6 700, 3 [illegible] white cells and 2 98[illegible] nucleated red cells per cu mm. Result of the fragility test was normal and repeated examinations of the blood for malarial parasites failed to reveal any The patient was discharged recovered 19 days after splenectomy

CASE 2—Girl, 8 was hospitalized because of pallor and weakness since early childhood At 4 years she had fever, jaundice abdominal pain and vomiting for a month In the past two years she had recurrent fever with abdominal pain and occasional cough An enlarging mass at the epigastrium had been noted for four months Among five siblings four had definit hemolytic anemia and the father had an increased icterus index Fragility tests of the blood of all the children with hemolytic anemia gave normal results

The patient's blood showed red cells 2 300 000 hemoglobin [illegible] per cent reticulocyte 31 6 per cent white cells 1[illegible] 400 [ra]tio of red to white cells 7[illegible] [illegible] Scleras and skin were [illegible] Spleen was enlarged and firm and liver was palpable fingerbreadth below the right subcostal arch After nearly month of supportive treatment she was splenectomized [Tw]enty two days later the ratio of nucleated red cells to white [cells] was [illegible] 402 2 0 Ten months after operation the anemia [and] jaundice were still present

[Ca]se 3—Girl [illegible] was hospitalized because of persistent [fev]er and mass at the left side of the abdomen Since the [age] of 1 month she had been a pale sickly and susceptible to [illegible] For two years she had had frequent [illegible] of fever [illegible] times with cough The father was [illegible] healthy

[illegible]

and greatly reddened in several areas Superficial excoriations were present at the oral commissures An apical systolic murmur was present Liver and spleen were not felt Reflexes and vibration sense were normal The finger nails showed vertical ridging and some were flattened, but there was no definite spooning

Laboratory data were urinalysis negative, fecal urobilinogen normal four stools negative for ova parasites and occult blood serology negative Blood studies showed hemoglobin 32 per cent (Sahli) erythrocytes 4 000,000 leukocyte, 10 200 platelets 400 000 and reticulocytes, 2 6 per cent The red cells showed considerable achromia with moderate variation in size and shape (Fig 61) Diameter varied from 4 5 to 10 5 microns average 6 9 microns The red cells were more hypochromic than microcytic and most of the leukocytes were multilobulated Icterus index was 6, serum protein was 6 08 Gm per cent Gastric analysis showed diminished secretion with complete achlorhydria after histamine Roentgenograms showed slight spasm of the upper esophagus Diagnosis was primary hypochromic anemia with the Plummer Vinson syndrome

The patient was given a bland diet to which at different times were added meat extracts powdered hemoglobin fresh beef blood and iron ammonium citrate all without appreciable response The iron was continued with the addition of 20 mg copper sulfate daily and after 12 days the hemoglobin rose to 56 per cent and red cell count to 4 300 000 She gained 8 lb and felt much stronger Diarrhea disappeared and dysphagia lessened She was discharged on a regular diet plus 8 Gm ferric ammonium citrate and 20 mg copper sulfate daily

Frequent observation until September disclosed maintenance of red cell and hemoglobin levels The perleche healed and the nails became normal Dysphagia lessened and the patient was able to eat ground meat despite her dislike for it Medication was reduced to 5 Gm ferric ammonium citrate and 10 mg copper sulfate daily In May 1934 the patient stated that she had discontinued her medication for the past eight months She was eating solid meat and green vegetables once daily felt well and had continued to gain weight slowly In October, 1934 although she had not taken iron for almost a year, hemoglobin was 75 per cent. Examination was negative except for an atrophic tongue

In June 1936, she stated that during the past six months her symptoms had returned and there were increasing diarrhea and dysphagia Examination revealed pallor and a red atrophic tongue Neurologic examination [illegible] e The red cell count was [illegible] and hemogl[illegible] 71 per

cent A month later the red cell count was 3 220 000 hemoglobin 77 per cent, leukocyte count 6 800 reticulocyte percentage 1 1, hematocrit reading 35 per cent mean corpuscular volume 109 cu microns and average cell diameter 8 10 microns

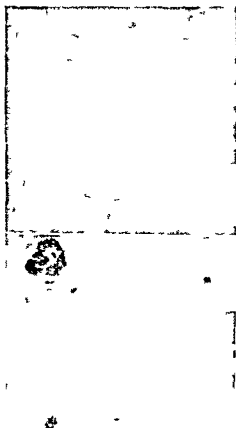


Fig 61 (top) —Bl d m J n 3 1933 H m l b 3 p e t d ll e t 4 000 000 d ll hyp h m d m m yt × 1,000
Fig 62 (bott m) —Bl od m Ap 26 1939 P mi d t h m gl b 34 per t d ll t 1 60 000 d ll w ll fill d w th hem gl bin and t d t b l g g l t w th m lt l b l t d n cl us 1 000

Icterus index was 10 Diagnosis was pernicious anemia and hospitalization advised, but the patient disappeared from observation for nearly three years

On second admission May 3 1939, there had been increase in dysphagia, return of exertional dyspnea and ankle edema in the previous nine months She had gradually lost 15 lb

Examination revealed extreme pallor, bilateral posterior cataracts perforated nasal septum atrophic glossitis unilateral perleche a just palpable liver edge systolic apical murmur minimal pitting ankle edema normal finger nail diminished vibration sense over ankles and tibia, and normal reflexes and gait

Urinalysis was normal Blood examination showed erythrocytes 1 260 000 hemoglobin 34 per cent leukocytes 4 400 reticulocytes 2 per cent platelets, 270 000 Stained smear showed microcytosis macrocytosis and multilobulated leukocytes (Fig 62) Price-Jones curves showed definite macrocytosis Icterus index was 14 Although there was still complete achlorhydria gastric analysis showed essentially normal volumes as compared with the previous extremely low volumes Sternal puncture showed megaloblastic hyperplasia with numerous giant metamyelocytes Roentgenograms were negative

A bland diet and 12 gr *ferrous sulfate* daily for 11 days had no effect Then liver extract intramuscularly in doses of 1 U S P unit daily was given for 11 days after which 6 units were given Peak reticulocyte response of 18 per cent occurred the twelfth day of liver therapy During the next two months with continued liver extract therapy the anemia improved consistently so that on August 4 the erythrocyte count was 4 550 000 and hemoglobin concentration 80 per cent She felt stronger and had gained 5 lb Vibration sense was improved Icterus index was 6 With continued liver extract therapy the blood counts were maintained at normal level but dysphagia continued Roentgenograms on Feb 4 1941 revealed two asymmetrical indentations of the cervical esophagus Above the indentations passage of barium was somewhat delayed and slight retention was present

In this case there seems to have been constitutional atrophic gastritis with gastric achlorhydria During a period of emotion dysphagia appeared because of which a diet deficient in iron containing foods was taken A chronic iron deficiency state appeared and a few years later probably as the result of either functional or organic involvement of the pyloric gl[illegible] the

intrinsic factor probably became greatly diminished with the result that pernicious anemia developed

[Cases also occur in which moderate macrocytosis and hypochromia of the red blood cells coexist In such patients there can be demonstrated a response to liver extract causing some increase in red blood cells and thereafter a response to iron chiefly affecting the hemoglobin level —Ed]

Pernicious Anemia of Pregnancy discussed by Elsa Segerdahl[7] (Uppsala) manifests itself during the last months of pregnancy or during the puerperium It is best characterized by the appearance of megaloblasts in the bone marrow and a specific response to liver treatment features in which it resembles true pernicious anemia Certain differences are manifest however in clinical course and blood picture Onset may be insidious but the more severe symptoms may occur precipitately Temperature is often fairly high and the spleen usually palpable Glossitis is common but neurologic symptoms are absent Gastric analysis usually reveals free hydrochloric acid thus resembling the pernicious anemia manifest in tropical macrocytic anemia sprue and Diphyllobothrium latum infestation The serum bilirubin is often slightly increased and urobilinuria has been noted

The blood picture may be similar to that of true pernicious anemia but variations are so frequent as to confuse diagnosis Frequently the color index is not increased but remains normal or definitely below 1 There may be only slight macrocytosis megaloblasts being absent from the peripheral blood In two cases observed by Segerdahl Price Jones curves showed a normal mean corpuscular diameter but a greater dispersion than normal Total leukocyte counts vary widely and leukocytosis is common Relative lymphocytosis is often absent The number of platelets varies

Response to liver therapy is sometimes slower than that in true pernicious anemia necessitating the use of larger doses However recovery is usually complete Relapses may occur with subsequent pregnancies

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[7] [illegible] 1 S 1 108 483 501 1941

pairment of the storage function of the cirrhotic liver for the antipernicious principle

Observations on Etiologic Relationship of Achylia Gastrica to Pernicious Anemia Experiments concerning the difference in the site of secretion of intrinsic factor in the hog and in the human stomach are reported by Herbert J Fox and William B Castle[1] (Harvard Univ) The blood forming activity of desiccated preparations of human stomach after arbitrary division into areas resembling the pylorus fundus and cardia portions of the hog stomach as defined by Meulengracht had a distinctly different distribution from that obtaining in similar areas of the hog stomach Thus the so called fundus and cardia preparations of the human stomach were highly effective whereas the pylorus was at best weakly active compared with ventriculin (N N R) in the dosage specified

It was not possible to develop an active fundus preparation of hog stomach by measures designed to prevent the local destruction of intrinsic factor to increase its secretion to activate a zymogen form or to potentiate intrinsic factor by contact with substances in the pylorus region of the stomach These facts contribute support to Meulengracht s assumption that the antianemic potency of the pylorus region of the hog stomach indicates it as a site of secretion of intrinsic factor in that animal Application of the same assumption to the present results with desiccated human stomach preparations leads to the conclusion that in man the fundus and cardia portions but not the pylorus region of the stomach are the important sites of formation or secretion of intrinsic factor Histologically the pyloric glands in the human stomach are found in an area extending along the lesser curvature to the angulus or about 6 cm from the pylorus but along the greater curvature they extend only a very short distance from the pylorus The cardiac glands are confined to an area a few ers wide adjacent to the border of the

esophageal mucosa The fundic glands occupy the rest of the stomach wall It is considered that division of the human stomachs used here was such that the pylorus preparation may have contained a considerable proportion of fundic glands whereas the so called fundus and cardia preparations contained fundic glands only It is therefore obvious that in these human stomachs the fundus type of gland was associated with antianemic activity The weakly positive effect observed with the so called pylorus preparation may be ascribed to the presence of fundic glands

According to this evidence, the site of secretion of intrinsic factor as defined by the hemapoietic activity of desiccated human stomach preparations, corresponds to the site of the degenerative process in the stomach in addisonian pernicious anemia in which disease the intrinsic factor is deficient These observations suggesting the relative insignificance of the pyloric gland organ as a source of intrinsic factor in man are in agreement with previous observation that pure duodenal secretion in man does not contain detectable amounts of intrinsic factor Thus with the exception of the recent report of Schenken Stasney and Hall all the observations which have been made on man point to the fundic gland area of the human stomach as the important source of intrinsic factor The evidence becomes contradictory only when conclusions which undoubtedly obtain for the hog are directly translated to man

Because the cardia of the human stomach is apparently an active site of secretion of intrinsic factor gastric resections in man which preserve this portion of the stomach should theoretically provide a source of intrinsic factor for the patient

Experimental Studies on Production of Pernicious Anemia by Operation on the Digestive Tract of dogs are reported by Svend Petri, Flemming Nørgaard Hans Jensenius and Erik Thyssen (Community Hosp Co

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penhagen) The following operations were performed total gastrectomy plus resection of the Brunner gland area in 12 animals (1 adult and 11 pups) resection of the pylorus and Brunner gland area in 12 (5 adults and 7 pups) resection of the pylorus and duodenum in 1 adult dog and resection of the pylorus Brunner gland area of the duodenum and distal two thirds of the small intestine in 3 pups

These operative measures constantly induced changes characterized as chronic subpellagra and acute or chronic pellagra In all animals except one subpellagrous dog there also developed anemia of various types and degrees but in no instance did the operations result in experimental pernicious anemia However in two of the three pups subjected to resection of the pylorus Brunner gland area of the duodenum and distal two thirds of the small intestine there did occur moderate anemia which was hyperchromic and macrocytic The postoperative anemias occurring after the first three types of resections fell into the following groups (1) hypo normo- or hyperchromic anemia (2) isolated hypochromia or (3) hypochromic polycythemia Anemia failed to develop in one animal

There was an apparent correlation between the age of the animals at operation and the degree of pellagrous changes In adult dogs only a state of subpellagra was obtained in pups pellagra was a constant result Correspondingly the pups often died spontaneously while adult dogs were killed Age also seemingly influenced the frequency and type distribution of the anemias Macrocytosis was observed only in pups whereas hyperchromia occurred in both age groups

Central nervous system changes in pups as well as in adult dogs were characterized by loss of cells degeneration of ganglion cells and medullary sheaths glia proliferation sclerosis of the blood vessels and edema Such changes appeared within the entire central nervous system including the retina and in the spinal gang [illegible] varied in degree and localization with the

type of operation performed and the course of the animal's illness The most severe changes in the gan lion cells occurred in the medulla oblongata pons and brain stem and were less pronounced proximally to this region (in the cerebrum) and distally (in the spinal cord) Medullary sheath degeneration was most pronounced posteriorly and centrally in the lateral columns of the spinal cord, less pronounced in the posterior columns and slight in all other columns

Failure to produce experimental pernicious anemia is explained by the authors on the basis that (1) the operations do not represent that combination of lesions of the stomach and intestine which jeopardizes the formation of the antipernicious anemia principle (?) the extent of operative measures has not been sufficiently great or (3) the prevailing conception concerning the intrinsic factor and thus the way the active liver principle is formed is erroneous

Prevention of Sensory Neuron Degeneration in the Pig, with Special Reference to Role of Various Liver Fractions Maxwell M Wintrobe Cecil Mushatt Joseph L Miller Jr Lawrence C Kolb Harold J Stein and Hermann Lisco[3] (Johns Hopkins Univ) report that abnormal gait and degenerative changes in peripheral nerves spinal ganglions and the posterior funiculi of the spinal cord developed in pigs deficient in factors other than thiamine riboflavin and nicotinic acid but did not occur when desiccated whole liver or brewers yeast was fed Wheat germ with alfalfa meal was not as effective in preventing sensory neuron degeneration as liver or yeast

The various fractions obtained during the manufacture of antipernicious anemia liver extract were assayed for their value in protecting the nervous system The fraction used in treatment of pernicious anemia was the most effective of all those tested, but relatively large amounts were required The value of the extract was not increased by parenteral administrati

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Growth was better when the antipernicious anemia extract or the press cake fraction was given than when other fractions were used but was not as satisfactory when the whole dried liver or a mixture of all the fractions was fed Furthermore convulsions and anemia developed in pigs fed these fraction

It should be noted that all animals ex pt those given yeast throughout the experiment rec ived upplements of thiamine alone or thiamine riboflavin and nicotinic acid in amounts adequate to prev nt d ficien ies of these substances

[The interest in this article attaches to th fact that degenerative chan es of the spinal cord occur in per u anemia and can be arrested completely by a lequate therap w th l ver or stomach preparations. See the following article – Eds]

Treatment of Pernicious Anemia Nine Year Study of Maintenance Requirements with Note on Efficacy of Purified Liver Extracts in Control of Neural Lesions Maurice B Strauss Arthur J Patek Jr Frederick J Pohle Herbert J Fox and Joseph H Burchenal[4] (Harvard Univ) analyzed the blood levels of 80 patients with pernicious anemia who received liver extract in varying amounts and at varying intervals during a five to nine year period Minimum length of any one mode of treatment was one year During the first part of this study the liver extract originally described by Strauss Taylor and Castle was used in uniform dosage of 10 cc per injection at one to four week intervals (The authors judge that 1 cc of this material has the approximate hemopoietic effect of 1 U S P unit of Solution Liver Extract Crude Lilly) Average red cell counts for patients receiving injections at intervals of one two three and four weeks were 4 780 000 4 720 000 4 850 000 and 4 750 000 and hemoglobin levels were 91 92 94 and 91 per cent respectively (100 per cent being equivalent to 15 6 Gm per cent) To facilitate comparison the patients were divided into six groups each group consisting of patients who received

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injections at different intervals (see table) It is apparent that varying the interval between injections from one to four weeks had no effect on either the red cell count or the hemoglobin level

EFFECT OF VARYING THE TIME INTERVAL BETWEEN INJECTIONS OF LIVER EXTRACT

PATIENTS	LIVER EXTRACT GIVEN AT EACH INJECTION CC	INTERVAL BETWEEN INJECTIONS WK	AV CAPILLARY RED CELL COUNT $\times 10^6$	AV CAPILLARY HEMOGLOBIN %
24	10	1	4 8	91
	10	2	4 8	95
18	10	1	4 8	92
	10	3	5 0	93
14	10	1	4 7	92
	10	4	4 7	94
49	10	2	4 7	93
	10	3	4 9	95
47	10	2	4 7	95
	10	4	4 8	95
48	10	3	4 9	95
	10	4	4 7	93

In 1938 three changes were made a uniform interval of four weeks between injections was adopted for all patients a shift was made from the relatively dilute type of liver extract previously used to Solution Liver Extract Purified Lilly containing 15 U S P units per cc and blood for examination formerly obtained by ear lobe puncture was removed by venipuncture without stasis It has been pointed out that in pernicious anemia at least ve us blood contains approximately 5 per cent less hemo lo and 250 000 fewer erythrocytes per cu mm than capil ry blood The amount of extract given at each inje ion was 10 15 20 or 30 units The average red cell nts maintained with each of these doses were 4 54 00 4 470 000 000 and 4

520 000 and the hemoglobin levels were 85 87 87 and 86 per cent respectively At the end of 1939 the amount of extract given 45 of the patients was increased by 50 per cent This procedure had no effect on the red cell count and hemoglobin level

In the first part of these observations no case of blood relapse occurred with the increased interval between injections and in the second part there was no statistically significant improvement in any patient s blood values with the 50 per cent increase in dose

Additional evidence of the adequacy of the treatment is to be found in the facts that no patient with subacute combined degeneration of the spinal cord suffered a neural relapse and that no patient without spinal cord manifestations developed neural lesions during the observation period The concentrated liver extract has been as effective in controlling the neural lesions as the less purified extracts previously used

When injections of 10 cc crude extract or 10 U S P units of purified extract was given at three to four week intervals certain patients felt less well during the third or fourth week after injection and during the period immediately preceding the next injection and a few actually had some subjective manifestations of glossitis that were abolished after the injections

The authors have now adopted a uniform maintenance dose of 15 U S P units of purified liver extract every four weeks for all clinic patients Eighteen months of this regimen has revealed no objective or subjective relapses in the blood gastro intestinal or nervous systems

The following criteria have been established for determining adequacy of treatment (1) If the red cell count is persistently under 4 000 000 greatly augmented doses of liver extract are given at short intervals such as 30 75 U S P units weekly for two or three months if this results in consistently higher blood values it is concluded that previous therapy was inadequate (2) If glossitis occurs treatment is considered inadequate irre of high red cell levels (3) If neural lesions

progress unfavorably the treatment is considered in adequate irrespective of red cell counts (4) If the patient lacks what he considers a satisfactory sense of well being on any given amount of treatment and re gains a feeling of better health when, unknown to him he is receiving a larger amount of extract, the original treatment is regarded as inadequate

Liver Dosage in Pernicious Anemia and considera tion of failure of quantitative storage of hemopoietic principle are discussed by William B Seymour, Robert W Heinle and Franklin R Miller (Western Reserve Univ) Although some storage of the hemopoietic prin ciple may take place patients with pernicious anemia generally do not remain in remission as long when treated with single massive doses as when they receive the same total dose in smaller amounts at spaced in tervals Nine patients in remission were treated with massive doses of liver extract receiving 55 140 U S P units of liver extract parenterally in 10 to 30 days after which no liver or liver extract was given until evidence of relapse occurred In six relapses occurred far in advance of the time calculated for the intermittent dose method In three the interval of remission was about the same indicating considerable variation in a patient s ability to store liver extract

Effects of massive doses of liver extract given 13 patients in relapse also were studied Duration of the actual remission cannot be compared with that which would have resulted if treatment had been instituted during remission since there is no method of calculating how much liver extract was utilized before remission was attained These patients were given 90 380 units of liver extract intramuscularly in 10 to 30 days Maximal reticulocyte response and rapid increase in red blood cells and hemoglobin occurred in each case It is evi dent that these patients were able to attain and main tain remission for longer periods than if liver extract had been given in dosage sufficient only to produce a

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maximal reticulocyte response All attained remission blood levels and remained in remission for 13 to 29 weeks without further treatment

The variation in a patient's ability to store liver extract probably depends on the fact that pernicious anemia is the result of a relative and not necessarily an absolute deficiency of gastric intrinsic factor The cogency of this argument was demonstrated in two patients with mild pernicious anemia who were maintained in remission for long periods merely by augmenting the extrinsic factor in the diet The fact that addition of extrinsic factor improves the formation of hemopoietic principle has been interpreted to be the result of a mass action chemical phenomenon Since intrinsic factor added to extrinsic factor equals hemopoietic principle increasing extrinsic factor causes an increase in the formation of hemopoietic principle even though the intrinsic factor is present in less than normal amount

Thus the variation in amount of liver extract required by different patients is adequately explained If the deficiency of intrinsic factor is relatively small and the amount of extrinsic factor in the diet relatively large less liver extract is necessary than if the reverse is true

Effect of Liver Therapy on Erythropoiesis as Observed by Serial Sternal Punctures in 12 Cases of Pernicious Anemia is described by L S P Davidson and James Innes[8] (Univ of Edinburgh) Each patient was in relapse Puncture was done before therapy was commenced and repeated once or twice after the first injection at intervals ranging from 6 hours to 10 days Differential counts of all nucleated cells were made and counts were made in which only nucleated cells belonging to the erythroblastic series were included It is on the basis of the latter that the authors make their observations

The authors distinguish four types of erythroblastic marrow cells in Romanowsky stained films Type I is a

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on the hemopoietic system a reversion of the normoblastic toward the megaloblastic blood picture may occur This supports the thesis that megaloblasts and normoblasts belong to one developmental series

Assay of Antipernicious Anemia Liver Concentrates by Use of an Isolated Bone Marrow Preparation Nello Pace and R S Fisher[7] (Med College of Virginia) attempted to provide a rapid easily available method for determination of potency of the concentrates The method depends on measurement of the migration of cells from isolated living bone marrow embedded in a coagulum of plasma to which various concentrations of liver extract have been added At certain concentrations of liver extract migration is increased

[The method described here has not yet received confirmation but if satisfactory it would be of great practical value in the assay of therapeutic materials —Eds]

HYPOCHROMIC ANEMIAS

The effectiveness of treatment of hypochromic anemias with inorganic iron compounds is well known the practical results are eminently satisfactory However many points concerning the mechanism of iron absorption from the gut its transport activity and *storage in the organism require further study Radioactive* iron is proving to be a valuable experimental tool in this as in other fields of investigation —Eds

Radioactive Iron Absorption in Clinical Conditions Normal Pregnancy Anemia and Hemochromatosis W M Balfour P F Hahn W F Bale W T Pommerenke and G H Whipple[8] (Univ of Rochester) discuss experiments which suggest that when the iron reserves are depleted the human being will absorb iron in relative abundance to the extent of 10 to 20 times normal Although the iron stores of the body are mainly in liver spleen and bone marrow these stores influence iron absorption in some obscure manner The iron content of the gastro intestinal mucosa is low and there [appea]rs to be little if any iron storage there but the

large cell (average diameter 18 μ) with a variable amount of cytoplasm usually deep blue The nuclei is pale and composed of a fine reticulated scroll like mass of chromatin Indistinct nucleoli may be present It corresponds to the megaloblast of Whitby and Britton and the pro erythroblast and megaloblasts A and B of Israels Type II average size 14 2 μ has basophilic or polychromatic cytoplasm and basophilic nucleus more deeply staining than in type I No nucleoli are present It corresponds to the erythroblast of Whitby and Britton and the normoblast A of Israels Type III averages 11 1 μ and has cytoplasm usually polychromatic The nucleus is deeply staining It seems to correspond to the late erythroblast or normoblast of Whitby and Britton and normoblast B of Israels Type IV averages 9 3 μ has polychromatic or orthochromatic cytoplasm and pyknotic nucleus It corresponds to the normoblast of Whitby and Britton

Within 6 to 10 hours after the initial injection of liver extract a change in cytology of the nucleated red cells occurs which consists of reduction in the mean size of the predominant cell type This is accompanied by a change in the nucleus which becomes deeper staining the chromatin strands tending to present an irregular lumpy appearance In other words cell type II increases in frequency at the expense of type I No definite evidence of amitotic division was seen and no increase in the number of mitotic divisions

After 32 to 72 hours the change is more pronounced Type I cells have become infrequent and the picture is dominated by type III cells In conventional terminology the megaloblastic picture has now become normoblastic

It seems to the authors that the rapidity of the change in bone marrow from a megaloblastic to a normoblastic picture supports the view that normoblasts or type IV cells can be derived directly from megaloblasts and that liver extract stimulates this change They believe also that under conditions of prolonged and severe

able number of myelocytes and polymorphonuclear leukocytes the proportion of myelocytes being increased In all cases the proportion of immature erythropoietic cells to normoblasts was greatly increased Clinical symptoms were relatively mild in this group the illness was sometimes of long duration and spontaneous remissions were not unknown Leukopenia and thrombocytopenia were inconspicuous or absent and hemorrhages and infections occurred infrequently Pigmentation of the skin was considered a complication and less frequently hemochromatosis In some cases this type of anemia appeared to be a temporary phase in the development of other disorders of the hemopoietic system

The second group consisted of 11 cases there was hypoplastic marrow (aplastic anemia) Clinically the duration of illness was shorter than in the previous group the symptoms especially hemorrhage were severe and spontaneous remissions occurred infrequently Six patients were examined at autopsy Conspicuous pallor was present in all Unusual yellowness of the subcutaneous fat was noted in four of the six External hemorrhages varied from petechiae to large subcutaneous ecchymoses (in three cases) Ulcers of various types were present in four cases The spleen varied from 110 to 200 Gm and the liver from 710 to 1 890 Gm in weight The bone marrow was completely fatty fatty with scattered red areas or mottled red yellow The proportion of fat cells to hemopoietic cells was greatly increased In several cases there were strands and small groups of hemopoietic cells mostly erythropoietic primary erythroblasts lymphocyte like cells and relatively few normoblasts almost all with basophil cytoplasm occasional myelocytes almost all eosinophil and occasional polymorphonuclear leukocytes were seen The immediate cause of death in most of this group appeared to be a pulmonary complication

The third group consisted of 14 cases with immature cellular marrow (chronic granulocytopenia) as the most characteristic symptom The bone marrow contained

OTHER ANEMIAS

The articles included in this section complete those dealing with anemias. The first two articles on refractory anemia or conditions which have been called by others aplastic anemia, aleukemic leukemia or nonleukemic myelosis deserve careful study here and in the original. They represent the best modern statement on this subject, admittedly confusing in terminology and disappointing regarding response to therapy. The suggestive relation of these anemias to cyclic compounds is a reminder of fortunately rare but grave potentialities —F Is

Refractory Anemia *I Clinical and Pathologic Aspects*—R R Pomfoid and C P Rhoads[1] (Rockefeller Inst New York City) report on 58 cases of anemia which proved resistant to any form of treatment except blood transfusions. This series was divided according to the histologic appearances in the section of bone marrow into four groups

The first group consisted of 31 cases and the main characteristic was a partly mature cellular marrow (pseudo aplastic anemia). In six autopsies of this type of refractory anemia there was some pigmentation. In only one case was there slight enlargement of the mesenteric and mediastinal glands. Average weight of the spleen was 160 Gm. Extramedullary erythropoiesis was much more prominent than leukopoiesis. The weight of the liver varied from 1 500 to 2 160 Gm; in four cases there was fatty degeneration or infiltration at the centers of the lobules. There was slight or considerable hemosiderosis in five of the six autopsies. The bone marrow differed least from normal. The degree of cellularity varied from a proportion of fat to hemopoietic cells that appeared almost normal to a densely cellular marrow without visible fat cells. Under low magnification this type of marrow was readily distinguished from the hypocellular type by the degree of cellularity and from the immature cellular type by the presence of considerable but varying numbers of eosinophil cells. Under higher magnification there was in every case a consider

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senting symptoms were those of any anemia On admis sion the liver was just palpable in three patients and just below the umbilicus in the fourth the spleen was not felt in one was just palpable in two and below the umbilicus in the fourth One patient had enlarged lymphatic glands in the axillae and groins Characteris tic features of this group were splenomegaly anemia fibrosis or sclerosis of the marrow and extensive extra medullary hemopoiesis the hemopoietic tissue usually containing conspicuous numbers of megakaryocytes The bone spicules of the marrow appeared thicker than usual and somewhat increased in number The marrow was patchy certain areas consisting almost entirely of pale eosinophils apparently fibrous tissue containing in its meshes a few scattered hemopoietic cells other areas consisted of moderately hyperplastic hemopoietic marrow of the partly mature type with little or no fat The hemopoietic cells were hemocytoblasts primary erythroblasts normoblasts myelocytes and polymorpho nuclear leukocytes with a relative increase of immature forms the number of megakaryocytes usually appeared distinctly increased Among the hemopoietic cells were fairly numerous oval and spindle shaped cells apparent ly fibroblasts and an increase of pale eosinophil ap parently fibrous tissue In certain cases the fibrous tissue appeared condensed with much closely packed deeply basophil material this was sometimes matted together and had the characteristic appearance usually associ ated with the term myelosclerosis

In any of the four major groups the onset of a remis sion of refractory anemia is usually indicated by an increase in the white cell count color index and mean corpuscular volume Remissions may be complete or incomplete When they are incomplete the blood picture resembles closely that seen in the mild macrocytic anemia of liver disease

II Etiology and Treatment—R R Bomford and C P Rhoads (Rockefeller Inst New York City) pre

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large numbers of erythroblasts and on superficial examination presented an appearance not unlike that of lymphatic leukemia There was usually no more than moderate anemia but severe and prolonged granulocytopenia often with considerable numbers of immature white cells in the peripheral blood stream Thirteen cases were examined at autopsy In eight areas of cellulitis or necrotic ulceration were present at death Average weight of the spleen was 235 Gm and of the liver 1 775 Gm The bone marrow in six cases was deep red and apparently hypercellular in all bones of the trunk Low magnification showed mostly basophil staining cells with the dark nuclei of normoblasts standing out conspicuously either singly or in groups No uniformity in appearance density of arrangement or size was observed Under higher magnification there were numerous hemocytoblasts and early primary erythroblasts in some cases with some late primary erythroblasts and normoblasts In other cases there were large numbers of smaller cells some resembling lymphocytes some resembling plasma cells and some being undoubted primary erythroblasts There were few normoblasts in these cases Almost invariably eosinophil myelocytes were present The appearance was similar to that of lymphatic leukemia because of the great predominance of lymphocyte like cells in the marrow The immediate cause of death appeared as in the two previous groups to be lung complications Average duration of the illness was relatively short The most prominent clinical feature was the occurrence of areas of necrosis and infection particularly in the neighborhood of the mouth and anus A remission occurred in one case only

The fourth group was composed of four cases with fibrosis sclerosis and giant cell hyperplasia of the marrow (myelosclerosis) as the most prominent clinical and differential symptom Duration of illness was relatively short and the outcome uniformly fatal The most prominent clinical feature was progressive and considerable enlargement of the spleen Ire

observed in examples of all four types of refractory anemia and an increasing degree of macrocytosis usually indicated onset of a spontaneous remission This macrocytosis as judged from the appearance of cells in films is associated with relatively little anisocytosis and very little poikilocytosis It apparently is unlike the variety found in pernicious anemia but like that seen in liver disease and in the type of anemia associated with myxedema

Marked pigmentation of the skin was seen in three cases and was associated with fibrosis of the liver with presence of pigment in the pancreas and other organs and in one case with diabetes Lesser degrees of pigmentation of the skin were noted in nine other cases In all these cases biopsy of the marrow showed the partly mature cellular type Liver function tests indicated impairment of hepatic function in 4 patients and in 14 of 26 one or the other of the three tests used was abnormal Apparently the impaired liver function in these patients was not merely secondary to the anemia since its occurrence showed no relation to the severity of the anemia The rate of excretion of fecal urobilinogen was increased above normal levels in some cases of all four types of refractory anemia and in half the patients examined Evidence of a considerably increased rate of hemolysis was found in a number of cases and a slight increase was probably present in all Hemolysis or the injection of hemoglobin in otherwise normal organisms leads to a compensatory hyperplasia of the bone marrow Hyperplasia was present in a considerable proportion of the patients at the time of biopsy but in comparatively few at the time of autopsy Possibly hemotoxins produce a hemolytic anemia but for some reason the compensatory hyperplasia of the bone marrow fails or is insufficient Furthermore hemotoxins possibly destroy not only circulating red cells but also developing cells in the marrow thus producing hypoplasia or one of the other changes seen in the bone marrow at autopsy

sent an analysis of 66 cases to determine possible important factors in the etiology of this condition Careful examinations of race sex age and family history indicated that these factors apparently have no influence on occurrence of the disease Four patients had a history of an endocrine disorder two were eunuchs and two had suffered from hyperthyroidism One patient developed hemochromatosis with diabetes during the anemia but this appeared to be a complication of the anemia In four women the first symptoms of their disorder appeared at or near the menopause in two more there was a history that the symptoms were more severe at or shortly before the time of menstruation There is no positive evidence of any relationship to endocrine disorder in these figures but the association with eunuchoidism menopause and menstruation merits further investigation Incidence of achlorhydria was below the normal Slight atrophy of the mucous membrane of the edges only of the tongue was seen in a few instances No disorders of the nails or nervous system were observed

Half of the patients were known to have been exposed to potentially hemotoxic substances in the form of aromatic hydrocarbons and one to roentgen irradiation and radium therapy Concerning the effects of sunlight and ultraviolet light six patients appeared to be worse after exposure to sunlight in one of them purpura and bleeding from the gums began suddenly after exposure to sunlight and in another exposure to sunlight on several occasions produced nausea fever and headache In one patient treatment with Alpine light was followed by nausea and palpitation and another patient felt better when treatment of this kind was abandoned The history of reactions after exposure to natural sunlight raises the question whether these patients who often excrete increased amounts of coproporphyrin I may have had a light sensitivity owing to presence of porphyrin in the skin and analogous to that seen in prophyria Slight or moderate degrees of mac [illegible] is were

be given at one time Whole unaltered blood from a donor of identical group given rapidly by a multiple syringe method appears to be the best procedure Splenectomy must be considered only as a last resort in only a small group of patients There are occasional patients with marrow of the partly mature cellular type in whom hemolysis as indicated by increased excretion of urobilinogen high reticulocyte counts and quick disappearance of the effect of transfusion appears to be particularly rapid In these the rate of hemolysis may be diminished by splenectomy and the effect of transfusions may thus be prolonged

Hypoplastic Congenital Anemia In recent years there have appeared reports of a peculiar form of anemia in infancy which does not conform to any accepted classification The condition is characterized by a hypoplasia rather than an actual aplasia of the marrow elements Erythropoiesis only is affected leukocyte and platelet counts are normal or only moderately diminished Hemorrhagic diathesis is absent Customary dietetic or medicinal measures were without effect in the cases reported and life was maintained only by repeated transfusions Blackfan and Diamond observed four such cases and mentioned four others Josephs reviewed their report and cited two cases of his own In all of these cases there was no evidence of blood destruction and no sign of regeneration Both of Josephs patients died when transfusions were discontinued Rinvik recently reported two similar cases in which both patients progressed relatively well with repeated transfusions Irwin Rubell[3] (Chicago) reports a case demonstrating a severe form of this anemia in which in addition to marked reduction of the erythropoietic elements the segmented leukocytes were almost nonexistent and the thrombocytes were much reduced The case was differentiated from true aplastic anemia only by its progress

The outstanding feature was an apparent inability of

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A working hypothesis of the etiology of refractory anemia is therefore that the disorder is due to a conditioned susceptibility to toxic substances usually exogenous or endogenous aromatic hydrocarbons, associated with hepatic dysfunction, a failure of biochemical mechanisms of detoxication and the circulation of hemolytic substances and that these hemolysins cause either an abnormal form of hemolysis and thus an abnormal reaction in the marrow or that they destroy both circulating red cells and developing cells in the marrow thus producing hypoplasia or other abnormal forms of marrow

Since the etiology of refractory anemia is not definitely established treatment must necessarily be empiric and unsatisfactory The single measure which appeared to be of most benefit was to remove patients from exposure to toxic substances Direct and detailed inquiry should be made about the patient s work habits home environment and consumption of medicine if any exposure to a potentially toxic substance particularly any substance containing a benzene ring is discovered this should immediately be terminated Habitual consumers of sedatives and analgesics should be induced if possible to abandon these drugs completely If these drugs are needed they should be limited to bromides codeine and if necessary preparations of opium In some patients of this series the condition deteriorated after single doses of pyramidon and similar drugs Strong sun light ultraviolet light and therapeutic roentgen irradiation must be avoided The diet should include meat fresh fruit vegetables and milk At least one prolonged course of injections of liver extract in as unrefined a form as possible should be given every patient Prolonged courses of large doses of bakers yeast 90 120 Gm or more by mouth daily are worthy of trial Blood transfusions are justifiable in every case when they appear necessary they should be continued no matter how poor the outlook may seem Because of post transfusion reactions not more than 500 c [illegible] would

sweating e pecially at night, poor appetite diarrhea and loss of 50 lb Physical examination disclosed pallor hoarseness white irregular areas surrounded by hemorrhages in both fundi reddened pharynx and edema and hyperemia of vocal cords enlarged lymph nodes in axillary cervical submental and popliteal areas There were moist rales at both lung bases and bronchial breathing on the right just above the nipple area Heart was normal except for soft systolic murmur Spleen and liver were not palpable Blood study showed red cells 2,540 000 hemoglobin 54 per cent white cells 3 200 neutrophils 68 lymphocytes 28 and monocytes 4 per cent platelets 12_000 Rare phagocytic monocytes contained numerous small bluish hyaline bodies with dark staining nuclei vaguely resembling Leishman Donovan bodies (Fig 63) Sternal marrow biopsy showed numerous monocytes and neutrophils containing similar bodies (Fig 64) as did reticulum cells from lymph node biopsy Blood culture was positive for Histoplasma capsulatum The patient grew progressively weaker with septic type of temperature and died in coma about four months after first symptoms appeared



Fig 64 —L ge b n l t d d th lial U t g n mer m par w tes t rn l bo

Autopsy revealed the typical lesion in liver spleen lung and intestines as a nodular granuloma resembling a gumma The smaller lesions were circular with a central portion of eosinophilic staining material Capillaries were patent even in the center which was necrotic Plasma cells lymphocytes and polymorphonuclears were scattered around the periphery Giant cells and epithelioid cells were not present The authors

out the period of ephedrine feeding (3 7 weeks or more) and returned to normal values in 7 to 10 days after cessation of drug administration Total leukocyte counts remained fairly constant

Two normal and two splenectomized rabbits which received 45 mg ephedrine sulfate daily by subcutaneous injection developed polycythemia with reticulocytosis within two weeks Daily injection of ephedrine into three rabbits which had a marked cobalt induced polycythemia produced further appreciable increases in their erythrocyte numbers

A significant polycythemia was produced in one human subject in two weeks by daily ingestion of 50 mg ephedrine sulfate The total leukocyte count did not increase or change significantly

Oral administration of 10 mg amphetamine sulfate daily to one splenectomized and three normal dogs caused significant increases in their basal red cell counts and hemoglobin percentages within 12 days

The slow onset of polycythemia following the commencement of daily ephedrine administration in these experiments as well as its slow regression on cessation of the drug indicates a probable true increase in erythropoiesis This interpretation is also supported by the reticulocytosis observed during these experiments The fact that splenectomized animals responded in the same way as normals to ephedrine or amphetamine also supports the belief that these drugs stimulate red blood cell production As to the mechanism by which ephedrine stimulates bone marrow the most plausible explanation seems to reside in a reduction of blood flow to this tissue through vasoconstriction with a consequent diminution of its oxygen supply The authors have previously shown that choline and its derivatives may have the opposite effect i e they depress excess erythropoiesis in polycythemic dogs probably by improving the blood supply to bone marrow since their action is blocked by atropine

Local hypoxia of bone marrow as the stimulus to

believe that some toxic process was re ponsible for the necro sis since small vessels were abundant and patent, surrounding the nodular granuloma and even passing through the necrotic area The appearance of healing granulomas found in the lung has not been described satisfactorily A marked poly morphonuclear cell reaction with abscess formation occurred which has not been described in previous cases

Histoplasma capsulatum can be grown on a variety of mediums, using either fresh or citrated blood from the patient Initial growth is slow in blood culture mediums incubated at 37 C The vegetative form of the fungus develops when the cells are subcultured on solid mediums and incubated at room temperature In a guinea pig infected by an intraperitoneal injection of the yeastlike form a slowly progressive infection was produced and at autopsy the typical pathologic changes of histoplasmosis were observed

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POLYCYTHEMIA

The next two arti les by Davis present evidence suggesting that experimental polycythemia can be produced by use of vaso constrictor drugs and therefore can be abolished by u e of va o dilator drugs The theoretical cause of these interesting results is the induced change in blood flow in the bone marrow with consequent decrease and increase respectively of oxygen ten sion in that tissue However confirmation is needed of the e experiments in which no data on possible changes in circulating blood volume are offered In some instances the fall of red blood cell values in response to vasodilator drugs appears to be more rapid than could be accounted for by depression of erythropoiesis alone —Eds

The Production of Experimental Polycythemia in Dogs Rabbits and Man by Daily Administration of Ephedrine and by Amphetamine in Dogs is reported by John Emerson Davis (Univ of Vermont) Daily oral administration of ephedrine sulfate to four normal dogs in doses of 2 5 to 5 mg per Kg body weight caused significant increases in the basal erythrocytes of all the animals in 10 to 15 days The red cell counts and hemoglobin percentages remained elevated through

(5) Am J Phy 1 134 1

of all six animals had been reduced considerably Ad ministration of the same dose of aminophylline had no effect on the red blood cell counts of normal dogs

Aminophylline (100 mg daily by stomach tube) had no effect on the red cell counts of three rabbits which had marked cobalt polycythemia

Mannitol hexanitrate was administered by stomach tube in 30 mg daily doses to five rabbits with cobalt polycythemia and one splenectomized dog with benze drine polycythemia Erythrocyte counts on all animals were reduced in three to four days despite continuation of the polycythemic stimulus The same dose of man nitol hexanitrate had no effect on erythrocyte counts of normal rabbits similarly studied

Choline hydrochloride 100 mg daily was given by stomach tube to three rabbits with cobalt polycythemia This proved to be as effective as mecholyl in reducing the erythrocyte counts

The daily ingestion of 1/4 lb of slightly cooked calves liver by one human subject who had experimental ephedrine induced polycythemia caused a gradual re duction of red cell count and hemoglobin percentage to approximately normal values after four days At this time both liver and ephedrine were discontinued following which the erythrocyte count climbed toward a polycythemic value and slowly returned to normal in about nine days Total leukocyte counts remained fairly constant throughout the experiment

The mechanism by which liver and vasodilator drugs depress excess hemopoiesis in polycythemic animals may be presumed to be the same for all such substances that are effective All appear to require three to four days to produce a maximal decrease of red cell count They do not decrease the red cell count in normal animals in the doses used The most probable mechanism of action is through vasodilatation and improvement of blood (and oxygen) supply to bone marrow This re duces the local anoxia which is presumably the immedi ate stimulus to polycythemia

polycythemia by ephedrine seems plausible from the standpoint of the time required to induce the full rise in the erythrocyte number, which agrees generally with the time required to induce polycythemia in dogs by exposure to low atmospheric pressure It may be assumed perhaps that the resultant immediate stimulus to polycythemia is the same in either case i e hypoxia of marrow

According to Warren, bone marrow metabolism is not under nervous control in rabbits exposed to low atmospheric pressure It may therefore be assumed that ephedrine does not act through the nervous system but rather directly or marrow arterioles

The mechanism of the production of polycythemia by amphetamine in dogs is probably the same as that of ephedrine since the responses of the red cell counts are the same for each drug

Depression of Experimental Polycythemias by Various Substances in Dogs, Rabbits and Man John Emerson Davis[6] (Univ of Vermont) reports that daily subcutaneous injection of 0 5 mg per Kg of acetyl beta methylcholine (mecholyl) significantly depressed the high red blood cell counts in four rabbits with cobalt polycythemia two splenectomized and one normal rabbit with ephedrine induced polycythemia two dogs with benzedrine polycythemia and one ephedrine fed dog all despite continued hemopoietic stimulating measures In every instance the decrease occurred in three or four days Total leukocyte counts were followed in the dogs, and did not change significantly during the reduction of red cell counts by mecholyl Hemoglobin percentages, however decreased with the red cells

Aminophylline was given orally in daily 100 mg doses to two dogs having ephedrine induced polycythemia two dogs with benzedrine polycythemia and two splenectomized rabbits with polycythemia induced by ephedrine and benzedrine Within three days and despite continuation of ephedrine or benzedrine the erythrocyte counts

(6) J Pharmacol & Exper Therap 73 16 169 1941

Symptomatic improvement usually followed venesection Length of remissions varied from a few days to a year In general blood lettings of 400 to 500 cc afforded subjective benefits for about two months Lesser quantities (350 450 cc) seemed more effective in this respect than larger (700-750 cc) Failure to effect any symptomatic change through venesection occurred five times in as many patients One of these had also on another occasion reported no change except for an increase in epileptic attacks to which he was subject This seems to have been merely a coincidental relation Two patients felt weak for about 10 days after 450 and 700 cc respectively had been taken and a third experienced a marked slump for about a month after withdrawal of 500 cc There were no other untoward symptoms or reactions

Clinical Studies with the Aid of Radiophosphorus III Absorption and Distribution of Radiophosphorus in the Blood of, Its Excretion by and Its Therapeutic Effect on Patients with Polycythemia Studies on four normal individuals and six patients with polycythemia are presented by L A Erf and J H Lawrence[8] (Univ of California) Previous studies have shown that radio phosphorus concentrates in the bone marrow and since it has a half life of 14 3 days it can constantly bombard with radiation a tissue in which it concentrates for this period It is this mechanism which is probably responsible for the favorable hematologic results obtained in patients with polycythemia In addition to hematologic improvement or remission these patients experience clinical and symptomatologic improvement Reduction of splenomegaly and hepatomegaly occurs frequently

Radiophosphorus was administered orally in three cases and both orally and intravenously in the remaining three Presumably in the latter cases the concentration of radiophosphorus did not reach sufficiently high levels following oral administration to reduce the production or releas of red blood cell The first evidence

(8) A I t M d 15 6 90 A u t 1941

Choline hydrochloride given orally in about 0 2 Gm doses thrice daily has been tried without success in human polycythemia vera by Carpenter and by Meyer and Thewlis

[The following two articles describe the use of venesection and of irradiation with radiophosphorus in treatment of polycythemia Since the disease is so easily controlled by venesection which produces by virtue of the loss of hemoglobin an iron deficiency with consequent depressed production of red blood cells this seems the method of choice However venesection in certain patients presents technical and psychologic difficulties which are obviated by use of x rays and now apparently of radiophosphorus It is illogical to use phenylhydrazine in treatment of polycythemia because although its action causes accelerated blood destruction, it also causes increased blood production Neither x rays nor phenylhydrazine can be regarded as entirely innocuous agents but there can scarcely be justification in our opinion for the use of lead in treatment of polycythemia as suggested by Falconer in the third article —Eds]

Use of Venesection in Treatment of Erythremia Arthur Andrews Holbrook[7] (Milwaukee) describes results obtained following 37 venesections performed on 10 erythremic patients Average blood letting yielded 420 cc Amounts taken varied from 125 to 750 cc The red cell and hemoglobin contents usually decreased a few days after treatment but occasionally the full effect was not realized for five to seven weeks In some instances venesection did not particularly affect hemoglobin and red cell values Viscosity curves paralleled the red cell curves Studies of blood volume after venesection in 10 instances revealed little change in total blood volume indicating rapid replacement of the quantity lost A paradoxical increase in total blood volume occurred after some venesections in three cases This is explained by the fact that with the improved circulation incident to treatment the dilution of the congo red effected is greater than it was previously, which constitutes an erroneous basis for comparison of results The greater the dilution factor the higher will be the reading of the blood volume That the volume is actually greater is not supported by Holbrook's experimental evidence

(7) W n M J 40 899 910 Octob 1941

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(8) Ann Int Med 15 6 90 Aug 1941

of significant decreases in the hemoglobin levels occurred approximately 100 days after an effective dose (this depended on the quantity and/or route of administration) of radiophosphorus had been administered Since radiophosphorus has never produced nausea vomiting or any clinical ill effects after its administration this form of therapy seems acceptable

A lesser excretion of radiophosphorus occurred in patients with polycythemia than in normal individuals. The reason is unknown It can only be assumed that the tissues of the patients with polycythemia had greater need or affinity for the phosphorus or that the radiophosphorus was retained by the tissues longer

Treatment of Polycythemia Vera with Lead Compounds Ernest H Falconer[9] (Univ of California) treated 11 patients with polycythemia vera with lead compounds orally and intravenously over one to five year periods Nine were relatively free from symptoms during treatment and were able to continue work Two patients with complicating thromboses were chronic invalids and unable to work treatment with lead is contraindicated in such cases No permanent or serious toxic effects have occurred in any of the 11 patients treated and no deaths have occurred in the series during the past five years One patient has disappeared from observation

INFECTIOUS MONONUCLEOSIS

The articles in this section are concerned with the clinical serologic and therapeutic aspects of infectious mononucleosis The distinction from acute leukemias in children and young adults is to be emphasized.—Eds

Infectious Lymphocytosis Carl H Smith[1] (Cornell Univ) describes two types of infectious lymphocytosis in children which are frequently confused with infectious mononucleosis and leukemia and presents cases illustrating the hematologic and clinical features of

(9) Am J M Sc 203 857 866 June, 1942
(1) Am J Dis Child 62 231 261 Aug, 1941

these types together with their differential features The terms acute and chronic infectious lymphocytosis are suggested for the conditions in the two groups of cases

Group 1 Acute Infectious Lymphocytosis—This group consisted of two children $3\frac{1}{2}$ and 6 years with unexpected and exaggerated lymphocytosis and a transitory hyperleukocytosis The course in each was benign and in neither was there lymphadenopathy splenic enlargement or clinical and physical signs of infectious mononucleosis or of leukemia. Examination of sternal marrow ruled out leukemia and the blood picture could be readily differentiated from that of infectious mononucleosis or leukemia The Paul Bunnell test was negative in both Each had been in the hospital before when there was a moderate leukocytosis with a neutrophilic response After subsidence of the hyperleukocytosis each child eventually showed moderate elevation of the white cells with absolute increase in lymphocytes In both cases nasopharyngitis was associated with this blood response as well as the other complaints characteristic of the second group Bacteriologic studies revealed the same type of organisms during every hospitalization but these could not be correlated with the type of blood response

Group 2 Chronic Infectious Lymphocytosis—In the nine cases of this group the common complaint was persistent low grade fever dating back to a well defined acute infection of the upper respiratory tract Pharyngitis and postnasal drip were the most common signs and there were no conspicuous lymphadenopathy and usually no splenic enlargement Symptoms were more conspicuous in six children under 6 than in three older ones The former presented an absolute increase in lymphocytes as compared with a relative increase in the latter In one older child however the febrile reaction had persisted for four years and numerous examinations had failed to determine the source of infection In several cases a preponderance of lymphocytes which

sometimes stained abnormally instead of giving an expected neutrophilic response caused suspicion of a blood dyscrasia As in the acute form the outlook was always favorable

Differential Diagnosis—Infectious mononucleosis an acute infectious disease occurs epidemically or sporadically and is characterized by a prodromal period of malaise anorexia and listlessness followed by fever pain in the back of the neck lymphadenopathy sore throat, splenomegaly and characteristic blood changes which affect chiefly the lymphocytes The febrile phase usually lasts one to three weeks and then subsides although glandular and splenic enlargement may persist The Paul Bunnell heterophil antibody test is positive In chronic infectious lymphocytosis the acute symptoms are usually milder and shorter and in contrast to infectious mononucleosis persist accompanied by low grade fever for months The Paul Bunnell test is negative In equivocal cases of infectious mononucleosis the morphologic character of the mononuclear cells serves as a more important differentiating factor The blood pictures of the two conditions overlap in that both small and intermediate lymphocytes with dark blue cytoplasm are present While large basophilic cells may appear in small numbers in infectious lymphocytosis they can readily be differentiated as lymphocytes Many of the mononuclear elements in infectious mononucleosis however may be so abnormal with regard to staining structure and size that classification is difficult The variability of the pathologic lymphocytes in the latter disease is in marked contrast to the more uniform blood smear in infectious lymphocytosis

Leukemia in childhood may for most of its course be unassociated with splenomegaly lymphadenopathy or leukocytosis so that the true nature of the disease is unsuspected Both chronic infectious lymphocytosis and the initial phases of leukemia may be characterized by prolonged low grade fever, listlessness fatigability, anorexia abdominal pain palpable cervical nodes and

a blood smear showing a predominance of lymphocytes While leukocytosis usually characterizes leukemia in childhood this disease may be associated with leuko penia for part or all of its course

In leukemia however with symptoms of the same duration as those in cases of chronic infectious lympho cytosis the blood would have shown marked anemia and a decrease in platelets While reduction of hemoglobin may occur in chronic infectious lymphocytosis such re duction is never as marked as in leukemia and the plate lets are not decreased In leukemia even with a normal white cell count occasional abnormal lymphocytes appear which possess the cytologic features of a lympho-blast The average lymphocyte in infectious mononucle osis is easily differentiated from the lymphoblast in leukemia The clumped chromatin of the nucleus of the large cells of infectious lymphocytosis may be readily differentiated from the leptochromatic nucleus of leukemia

Infectious Mononucleosis In 1936 Minot described three cases with acute thrombocytopenic purpura and high grade lymphocytosis (74 80 per cent) and many abnormal lymphocytes in the blood The patients aged 23 21 and 10 showed mild fever with slight generalized swelling of lymph nodes and two had enlarged spleen at the height of the disease In two cases the Paul Bunnell test was not done in the other it was negative All three patients recovered and had no recurrences in 1 to 3½ years Minot concluded that these cases are examples of purpura haemorrhagica with atypical white cell response rather than atypical infectious mononucleosis with pronounced thrombopenic purpura William Magner and E F Brooks (Toronto) report a case in most respects similar to Minot s except that this patient s serum showed presence of heterophilic antibodies characteristic of infectious mononucleosis

Youth 20 presented petechial hemorrhages on both legs the chest and the buccal mucosa There were inguinal lym

(2) Ca d M A J 4 3 40 July 194

phadenopathy slight splenomegaly albuminuria and gross hematuria *Blood* studies revealed great reduction in platelets and the leukocytic picture of infectious mononucleosis The Paul Bunnell test was positive in dilutions of 1 896 Clinical course was satisfactory Subjective symptoms were at all times mild No fresh petechiae appeared after admission Hematuria and splenomegaly had disappeared by the sixth day *Temperature* which had not risen higher than 99 2 F was normal from the *ninth day*, and the patient was discharged in good condition 16 days after onset of hematuria and purpura

Further Serologic Studies in Infectious Mononucleosis There are at least five technics for demonstration of heterophile agglutinins in infectious mononucleosis Because of overlapping sensitivity of these tests establishment of a set of values for a "normal control series is important for proper interpretation Using the simple tube test R Straus and M T Bernstein[8] (St Luke's Hosp Cleveland) investigated the heterophile antibody content of the serums of 76 patients with infectious mononucleosis and 248 persons without clinical infectious mononucleosis

Fifty nine of the 76 patients showed maximum serum heterophile agglutinin titers of 1 256 to 1 65 536 Maximum titers of 1 128 were found in nine thereby placing them in the borderline category In eight titers varied between 1 64 and 1 8 Such are usually referred to as seronegative cases of infectious mononucleosis

Multiple observations were conducted in 48 cases Most of them were first examined when the heterophile antibodies were either at maximum concentration or disappearing In eight patients examined within three weeks of onset maximum concentration had not yet been reached Subsequent observation in these cases suggested that antibody formation is relatively rapid It was noted that maximum antibody concentration at any given period of the disease may vary considerably among patients in keeping with experimental findings on antibody production in animals Rate of disappearance of antibodies from the blood stream is fairly uniform in all

(8) Am. J Clin P th 1 1 418 Mar h. 194

cases a marked decrease in agglutinin content occurring soon after establishment of peak concentration This rate of decrease tends to taper off in the lower concentrations In most cases antibody titer is as low as 1 64 or less within 150 days

Of the 248 controls 230 had titers of 1 64 or less 7 had a titer of 1 128 and 4 a titer of 1 256 Multiple observations in 39 revealed flat curves

The authors conclude that titers of 1 512 or more obtained with the simple tube test are diagnostic of infectious mononucleosis In cases in which serum sickness can be excluded titers of 1 256 or 1 128 are strongly suggestive but not diagnostic Titers of less than 1 128 do not exclude the disease Two or more determinations at weekly intervals to show the trend of the agglutinins are of more significance than a single observation especially in cases in which a rising or falling titer can be demonstrated

The Davidsohn differential absorption test is of diagnostic value especially in cases of infectious mononucleosis with borderline titers and in cases complicated by a history of therapeutic injections of horse serum In cases with low titers of heterophile agglutinins a negative differential test does not exclude the disease In cases with a higher titer of agglutinins the procedure is valuable as another confirmatory test

Treatment of Infectious Mononucleosis with Specific Convalescent Serum H C A Lassen and S Thomsen[4] compare results of treatment in 12 patients with severe infectious mononucleosis with specific convalescent serum with the outcome in 15 untreated patients 50 treated with nonspecific serum and 27 treated with neoarsphenamine injections Specific convalescent serum in doses of 60 to 300 cc intravenously brought rapid improvement in the general condition more rapid fall of the temperature to normal and a marked subjective feeling of improvement usually within one to two days after administration

(4) Ugesk f l g 102 774 9 July 5 1940

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(3) Am J Cl n P th 1° 174 182 M h 1942

months Sulfathiazole did not produce any appreciable change in the blood picture Previous experience with sulfanilamide in other patients was disappointing Sulfathiazole seems to be of definite value in shortening the symptomatic stage of this disease

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LEUKOPENIA AND MALIGNANT NEUTROPENIA

Relatively few articles on these conditions have appeared in the literature during the past year In addition to material in the two articles included here the occasional development of agranulocytosis as a result of sulfonamide administration has been reported —Eds

Role of Abdominal Distention in Leukocyte Exhaustion John Van Duyn II[7] (Syracuse N Y) reports four cases and cites two from a previous article which illustrate the association of leukocytic exhaustion with abdominal distention in the absence of severe infection The table compares the blood picture in these cases in which there was no severe infection (series 1) with cases showing a similar white blood cell failure but in which severe infection was present (series 2) In the former the blood picture is purely degenerative in the latter mixed degenerative regenerative The pure degenerative blood picture is characterized by low to leukopenic leukocyte counts normal to neutropenic neutrophil percentages absence of myelocytes normal to increased percentages of lymphocytes and monocytes and presence of eosinophils In the mixed degenerative regenerative picture regenerative elements are found such as neutrophilia presence of myelocytes monocytopenia and absence of eosinophils Prognosis in cases with pure degenerative shift is not unfavorable (Schilling) however with mixed degenerative regenerative shift the condition is fatal

In 5 of 20 cases of uncomplicated mechanical obstruction of the small intestine with distention the degenerative tendency was present In five cases of peritonitis and pneumonia in which there was leukocytic exhaustion with

(7) A h S g 44 239 3 F b y 194

Effect of Sulfanilamide on Infectious Mononucleosis Basing his opinion on a comparison of results obtained in treatment of 31 cases of infectious mononucleosis with sulfanilamide with those obtained in 30 similar cases in which no causal therapy was attempted S Thomsen concludes that while sulfanilamide therapy may shorten the course of the disease somewhat the difference in the cases observed is insufficient to warrant definite conclusions Histologic examination of tonsils removed either at necropsy or by tonsillectomy indicated that the throat disorder in this condition is due largely to mixed infection from the oral cavity by bacteria which invade the tonsils already greatly altered by the primary disease The infection causes a general purulent tonsillitis which often results in abscesses and necrosis This inflammation is essentially different from the mononuclear hyperplasia due to the primary infection The apparent effect of the sulfanilamide may result from an action on this secondary mixed infection rather than from any action on the primary disease Three cases are described in which combined treatment with sulfanilamide and specific convalescent serum resulted in rapid drop in temperature and disappearance of symptoms

Use of Sulfathiazole in Infectious Mononucleosis H T Hoffman H D Lees and B I Comroe[6] (Univ of Pennsylvania) studied 29 patients with infectious mononucleosis who showed positive heterophil antibody reactions 7 of whom were treated with sulfathiazole An initial dose of 1 Gm was given followed by 0 5 Gm every four hours for the first two days Dosage was then reduced to 0 5 Gm four times daily continued for four to eight days The results indicate that sulfathiazole is superior to any form of therapy previously used for this disease Clinically all the patients receiving the drug showed prompt improvement fever sore throat malaise and much of the adenopathy disappeared after four or five days In patients who did not receive sulfathiazole these symptoms persisted for two to four

(5) Ugesk f læger 10 ... 8 82 Jul 5 1940
(6) Am J M Sc ... 13 ... 1942

mixed degenerative-regenerative shift the degenerative elements were distinguishable from the regenerative Abdominal distention was present in all five cases The degenerative type of leukocytic failure may also be found with disease of the gastro-intestinal tract other than that associated with obvious abdominal distention e g typhoid and certain types of dysentery and colitis

Abdominal distention is concluded to be at least one important cause of the degenerative blood picture The actual mechanism of production is through absorption from the distended intestinal wall of some apparently nonbacterial toxic substance which acts either directly or indirectly as inhibitor of leukopoiesis Thus a low or falling white blood cell count with marked neutrophilic shift to the left and toxic granulations does not necessarily mean that the marrow is overwhelmed by infection that the patient s resistance is abnormally low or that the prognosis is poor It may be due to a purely degenerative influence

Preliminary Report on Treatment of Agranulocytosis with Sulfathiazole William Dameshek and Louis E Wolfson[8] (Beth Israel Hosp Boston) treated two patients with severe agranulocytosis with transfusions pentose nucleotides liver extract and large doses of sulfathiazole Both patients were in a critical condition with marked oral necrosis elevated temperature pulse and respiratory rates Initially no granulocytes were seen in blood films Recovery may have been due in part at least to the effect of the sulfonamide on sepsis which was almost certainly present thus allowing spontaneous leukocytic regeneration in the bone marrow to take place Sulfonamide drugs may be effective even in the complete absence of granulocytes

[This is an important therapeutic possibility for controlling the sepsis secondary to agranulocyto s or leukemia We are con v nced from personal exp rience that the sulfonamides are of value in such s tuations —Eds]

(8) Am J M S 03 619 8 3 J n 1942

COMPARISON OF TWO SERIES OF LEUCOCYTE COUNTS

Smear	Age	Sex	W B C	Neut %	Myel %	Lymph %	Mono %	Eosino %	Baso %	Nonfilamented Neut %	Strain on Marrow
Series 1 marked distention no severe infection											
1			3 200	60 7	0	21 0	17 0	0 7	0 7	93	Laparotomy and salpingitis
2			3 500	66 0	0	20 0	13 3	0 7	0	93	Parturition
3	30	M	5 400	65 7	0	19 0	12 3	2 3	0	95	Appendectomy
4	38	F	7 200	64 3	0	22 2	12 3	1 0	0	93	Appendectomy
5			6 700	56 3	0	30 3	9 3	2 0	0	94	Intestinal resection
6	50	F	3 300	31 3	0	53 0	11 7	1 0	0	94	Preoperative volvulus
Series 2 severe infection distention											
7	67	M	3 600	74 3	5 7	18 3	7 0	0	0 3	98	General peritonitis and carcinoma
8	23	F	3 900	91 0	2 3	7 0	2 0	0	0	93	General peritonitis
9	75	M	7 000	70 0	4 0	26 3	3 7	0	0	95	General peritonitis
10	66	M	2 400	47 0	4 5	52 5	0	0	0 5	98	Lobar pneumonia
11	7	M	8 800	82 7	2 3	17 3	0	0	0	95	Bronchopneumonia

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Histologic Classification —1 Stem Cell Lymphoma In lymph nodes an undifferentiated cell of mesodermal origin which as a result of unknown stimuli develops *the ability to differentiate into various forms of blood* cells is appropriately designated the lymphoid stem cell It is large 10 15 microns in diameter and has variably abundant pale staining amphophilic cytoplasm possessing a poorly defined often imperceptible outline When closely packed as in the center of a hyperplastic follicle the cells may seem to constitute a syncytium but when

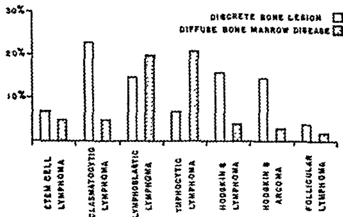


Fig 65—B [illegible] subgroup

more discrete intercellular bridges are sometimes noted The nucleus is large two to four times that of a normal lymphocyte is usually round and presents a thin but distinct border Chromatin is extremely delicate irregularly distributed and generally lacks condensation points There is however usually a single prominent vesicular nucleolus In most lymphomas these cells are so rare as to escape notice unless specifically sought but in a limited group they constitute the predominant element

2 Clasmatocytic Lymphoma *In contrast to the preceding group* with which it has been widely confused the cells in these tumors simulate normal clasmatocytes or

LEUKEMIAS LYMPHOMAS AND LEUKEMOID CONDITIONS

The first article in this section is an important contribution to the classification and clinical aspects of malignant lymphomas including Hodgkin's disease The authors conclude that the presence or development of leukemia cannot be predicted on the basis of morphologic changes in tissues On the other hand histologic study often yields information of prognostic importance The other articles in the section are concerned with various aspects of leukemia and leukemoid responses —Eds

Malignant Lymphoma Edward A Gall and Tracy B Mallory[9] (Massachusetts Gen l Hosp) present a cytologic classification of the malignant lymphomas Seven categories are delineated which differ from widely accepted classifications primarily in the subdivision into two types of what has generally been grouped under the heading reticulum cell sarcoma one in which the cells are highly undifferentiated and resemble lymphoid stem cells for which the authors have proposed the name stem cell lymphoma and a second in which the cells show recognizable features of differentiation in the direction of tissue phagocytes and has accordingly been termed clasmatocytic lymphoma It has also proved useful to divide the tumors showing clear evidence of belonging to the lymphocyte series of cells into lymphoblastic and lymphocytic types depending on whether immature or mature cells predominate Hodgkin's disease too has appeared divisible into lymphomatous and sarcomatous types Follicular lymphoma has been shown to be a form of malignant lymphoma and not as has been claimed merely an inflammatory process The nomenclature adopted for this study and the number of cases of each type were as follows

1. Stem cell lymphoma 56 cases } Reticulum cell
2. Clasmatocytic lymphoma 71 cases } sarcoma
3. Lymphoblastic lymphoma, 85 cases
4. Lymphocytic lymphoma, 135 cases
5. Hodgkin's lymphoma 193 cases
6. Hodgkin's sarcoma 36 cases
7. Follicular lymphoma, 42 cases

(9) Am J Path 18 381 4 9 May 194

Histologic Classification.—1 Stem Cell Lymphoma In lymph nodes an undifferentiated cell of mesodermal origin which as a result of unknown stimuli develops the ability to differentiate into various forms of blood cells is appropriately designated the lymphoid stem cell It is large 15 35 microns in diameter and has variably abundant pale-staining amphophilic cytoplasm possessing a poorly defined often imperceptible outline When closely packed as in the center of a hyperplastic follicle the cells may seem to constitute a syncytium but when

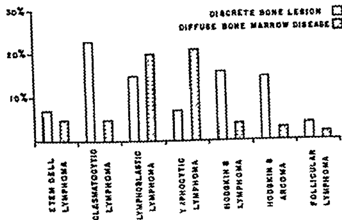


Fig 65.—B l m t by pe g f a h fg p

more discrete intercellular bridges are sometimes noted The nucleus is large two to four times that of a normal lymphocyte is usually round and presents a thin but distinct border Chromatin is extremely delicate irregularly distributed and generally lacks condensation points There is however usually a single prominent vesicular nucleolus In most lymphomas these cells are so rare as to escape notice unless specifically sought but in a limited group they constitute the predominant element

2 Clasmatocytic Lymphoma In contrast to the preceding group with which it has been widely confused the cells of these tumors simulate normal clasmatocytes or

monocytes from which they are often indistinguishable These cells tend to be smaller than lymphoid stem cells but are distinctly larger than lymphocytes varying from 14 to 22 microns in diameter The cytoplasm is abundant generally eosinophilic and its borders, though distinct tend toward irregularity suggesting ameboid propensities The marked phagocytic properties are usually limited to particles although engulfment of whole cells occurs Nuclei are frequently eccentric a few are round, more are oval and still others are reniform or even horse shoe shaped They present a moderately fine chromatin network nucleoli are rare

3 Lymphoblastic Lymphoma Predominant in these lesions is the lymphoblast This is a spherical cell which however frequently exhibits pseudopod like protuberances It is larger than a mature lymphocyte measuring 10 20 microns in diameter and presents a narrow basophilic cytoplasmic rim around a centrally placed round or slightly indented nucleus The nuclear border is sharp the chromatin rather evenly distributed and much less clumped than in mature elements imparting a vesicular appearance to the nucleus Nucleoli are infrequent Mitotic figures are usually numerous Specimens included in this group present stem cells in moderate numbers and in some considerable numbers of lymphocytes can be found The nodal architecture is characteristically obscured

4 Lymphocytic Lymphoma The predominating cell is indistinguishable from a normal lymphocyte A few stem cells and lymphoblasts are present but are not sufficiently frequent to confuse diagnosis. Mitotic figures are sparse and no multinucleated cells appear Nodal architecture, including sinus and follicle structure is characteristically obscured by the relatively uniform infiltration of small lymphocytes Stromal revision may be incomplete

5 Hodgkin s Lymphoma The pathognomonic elements of this lesion consist of stem cells frequently indistinguishable from those of stem cell lymphoma '

which tend strongly to develop large multilobed or multinucleated forms The specific cells vary in size ranging from 10 to 40 microns or more in diameter The cytoplasm is abundant and its staining reactions though usually intense are variable ranging from acidophilia to basophilia in different cases though relatively constant in the same case Single nuclei are large and round oval or slightly indented they are vesicular in appearance and contain chromatin without characteristic distribution In the majority single nucleoli are found which differ from those noted in the stem cell tumor in that they are not densely stained but are actually vesicular in appearance

In the multinucleated forms the nuclear masses may show narrow connecting bridges or may be entirely discrete In either case large nucleoli are usually evident in each nuclear mass and the nuclear masses are characteristically dissimilar in size and shape Even when each of the many nuclei is discrete they tend to overlap and remain clustered in the center of the cell Unipolar mitotic figures are easily found and multipolar mitoses are not unusual Mitotic activity is unusual however in any of the other cells composing the lesion The polycellular picture includes the usual components of various inflammatory reactions i e granulocytes (usually eosinophilic but frequently neutrophilic) lymphocytes plasma cells clasmatocytes and fibroblasts and the mono- and multicellular giant cells described by Sternberg and Reed

6 Hodgkin s Sarcoma Hodgkin s sarcoma differs from Hodgkin s lymphoma in the marked preponderance of Sternberg Reed cells over all other elements comprising the tumor Characteristically the lesion consists of large numbers of these cells without syncytial relations exhibiting marked variability in size and nuclear configuration Multinucleated cells predominate and mitotic figures are numerous Lymphocytes plasma cells and eosinophils though present are minimal in numbers and fibrosis rarely proceeds beyond the early background

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of strandlike collagen Densely scirrhous tumors do not occur *Monocytes and clasmatocytes are present* many of the latter attaining features simulating neoplastic change

7 Follicular Lymphoma This is manifest fundamentally by complete replacement of normal lymph node architecture by *multiple follicle like nodules of* varied size and approximation These are also present in regions of extranodal invasion *The structure of the nodal* reticulum is characteristically revised Trabeculae are obscured Surrounding each follicular node the reticulum meshwork *is obviously distorted and condensed by* the expanding follicle and the normally loosely arranged network with broad polygonal pulp spaces becomes compressed and the inter reticular spaces markedly elongated and narrowed Despite this condensation of interfollicular fibrils *actual fusion with production of collagen does* not occur The sinuses are evidently obscured by displacement of condensed fibrillar material into them The *sparse stretched attachments of follicles to the surrounding* framework allow for separation of the follicles from surrounding tissues in the *process of sectioning* This seeming *cracking off* of follicular from nodal substance is due to artefact but is sufficiently constant to serve as a *differentiating criterion It is observed relatively* uncommonly in other lymph node conditions

Clinical Studies—In 545 cases the disease most frequently *became evident in the fifth and sixth decades* except in Hodgkin s lymphoma which showed maximal incidence in the third and fourth decades Only three types *occurred with significant frequency in the first two* decades Hodgkin s lymphoma lymphoblastic lymphoma and lymphocytic lymphoma For the entire series the *proportion of men to women affected was* 2 2 1 Duration is recorded in the table

Lymph node enlargement was present in over 90 per cent of the subgroups *Fever occurred at some time* during the course in cases from all subgroups *Intermittent* fever of the Pel Ebstein type occurred with signifi

cant frequency (16 per cent) only in the two Hodgkin s types and was infrequent among the others General ized cutaneous infiltration appeared in 16 to 26 per cent of cases in all groups except the follicular lymphomas among which cutaneous lesions were unusual There appeared to be a significant group variation with regard to visceral predilection The gastro intestinal tract was more often involved in patients with Hodgkin s sarcoma stem cell and clasmatocytic lymphoma and exceptionally in follicular lymphoma Genito-urinary involvement was most common among the lymphocytomas less common in lymphoblastic lymphoma and Hodgkin s sarcoma and rare in the other types Pulmonary foci were most fre quent in Hodgkin s disease and comparatively rare in other subgroups

TOTAL DURATION (YEARS)

Type	Males		Females		Total	
	Av	Median	Av	Med	Av	Median
Stem cell lymphoma	1 4	1 1	2 5	1 3	1 7	1 1
Clasmatocytic lymphoma	2 3	1 0	1 9	1 2	2 1	1 1
Lymphoblastic lymphoma	1 4	0 5	1 4	0 6	1 4	0 6
Lymphocytic lymphoma	3 4	3 0	3 0	1 9	3 3	2 4
Hodgkin s lymphoma	4 3	3 1	3 7	3 8	4 2	3 2
Hodgkin s sarcoma	1 [illegible]	0 9	1 7	0 9	1 8	0 9
Follicular lymphoma	4 6	4 0	6 8	5 6	5 6	5 0

Obstructive phenomena were striking in follicular lymphoma less evident in clasmatocytic and stem cell lymphomas and considerably less among the remaining subgroups Ulceration secondary to neoplastic infiltra tion of skin or mucosa occurred most frequently with stem cell lymphoma and Hodgkin s sarcoma Peripheral edema and ascites appeared in over one third of the cases of follicular lymphoma and much less commonly in the remaining groups

Isolated skeletal lesions often solitary manifestations of the disease were recorded in one fourth of the patients with clasmatocytoma They appeared less fre

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Atypical cells tumor cells unidentified cells and blast forms appeared in the peripheral blood of almost two thirds of the cases of lymphoblastic lymphoma one third of those of lymphocytoma and one quarter of those of Hodgkin s lymphoma and sarcoma In only 6 to 14 per cent of the remainder were such phenomena ap parent

The authors conclude that the presence or develop ment of leukemia cannot be predicted on the basis of any constant morphologic criterion In fact often the blood picture is inconstant and varies from time to time during the course It seems more reasonable to consider lymphatic leukemia simply as a manifestation of an underlying lymphomatous process Similarly in the in terests of clarity it would seem judicious to discard such terms as lymphosarcoma (Kundrat) and leukosar coma since these too appear merely to represent tran *sient phases of malignant lymphoma and do not consti* tute disease entities

Hodgkin s Disease Ray E Burger and Edwin P Lehman[1] (Univ of Virginia) analyze 54 histologically proved cases There were 45 whites and 9 Negroes 32 were males and 22 females Age range was 4 70 in most cases onset occurred in the third decade There were no demonstrable predisposing factors in any case Heredity environment occupation and food appeared to play no important part Familial history was negative in all

Chest roentgenograms in three revealed changes con sistent with old healed tuberculosis in three more there was suspicion of tuberculous activity and in one there was concomitant pulmonary and miliary tuberculosis Thus in 12 9 per cent there was healed or active tuber culosis Blood cultures were made in three cases bru cella was demonstrated in one

Cervical adenopathy weakness fatigue weight loss cough dyspnea and backache were the commonest com plaints on admission in 10 cases there were no symp toms except adenopathy Average time between onset

(1) A b S g 43 839 849 N mbe 1941

quently in Hodgkin s and lymphoblastic lymphoma and Hodgkin s sarcoma and were distinctly unusual in the other types Presence of pathologic fracture varied directly with frequency of discrete bone lesions (Fig 65)

Of nonspecific changes in the peripheral blood, anemia was most important Erythrocyte counts of 3 500 000 or less were present in one half to one third of the patients with lymphoblastic Hodgkin s and lymphocytic lymphoma and Hodgkin s sarcoma in descending order of frequency Anemia was much less common in the cases of follicular clasmatocytic and stem cell lymphoma Profound anemia was recorded most often in the lymphoblastic and lymphocytic lymphomas with leukemic manifestations and in the terminal stages of Hodgkin s disease

Leukocytosis exceeding 12 000 occurred in 50 to 60 per cent of cases of lymphocytic and lymphoblastic lymphoma and Hodgkin s sarcoma It was less common with Hodgkin s clasmatocytic and stem cell lymphoma and unusual in follicular lymphoma Leukopenia with less than 5 000 cells was noted in 11 to 16 per cent of cases of lymphocytic lymphoblastic and Hodgkin s lymphoma It was rare in other types

Monocytes in excess of 10 per cent were recorded in one third of the cases of Hodgkin s lymphoma and sarcoma and one quarter of those with clasmatocytoma but rarely in the remainder Markedly diminished monocyte values occurred with lymphocytic and lymphoblastic lymphomas

Lymphocytosis was observed in 62 to 70 per cent of the cases of lymphocytic and lymphoblastic lymphoma Lymphocytopenia appeared in only 19 per cent of the Hodgkin s lymphomas and 13 per cent of the Hodgkin s sarcomas The remaining groups generally exhibited normal values Variations in the number of eosinophils were considered to be lacking in pertinent diagnostic value Eosinophilia was not a prominent feature in Hodgkin s disease

much more common than the classic Pel Ebstein variety which occurred in only eight patients in this series

Average survival time from onset of symptoms was 26 months Treatment in most cases consisted of repeated roentgen irradiation of involved tissues aided with blood transfusions and general measures Treated patients have on the average survived nearly three times as long as untreated patients Regardless of the type of therapy Hodgkin s disease has proved an almost universally fatal malady in the proved cases A few isolated cures have been reported In some cases the patients lived 20 years or more

Chronic Leukemia in Three Sisters John H Hornbaker[3] (Hagerstown Md) reports two cases of lymphatic and one of myelogenous leukemia occurring in three sisters Although familial leukemia has been described a number of times most reports concern only two members of a family There is insufficient evidence to explain the occurrence of familial leukemia on the basis of heredity except for the known hereditary factor in cancer of which leukemia is now usually regarded as an example

CASE 1 —Woman noted purpuric spots on the legs and occasional oozing of blood from the nose in the summer of 1927 when 39 years old In October 1927 and February 1928 she had severe bleeding from the nose and mouth and purpuric spots appeared over the entire body These underwent occasional remission but she noted a tendency to bruise easily Examination in April 1928 revealed tachycardia moderate pallor lymphadenopathy in the cervical supraclavicular axillary and epitrochlear regions spleen questionably palpable and no purpura Blood studies revealed erythrocytes 3 690 000 hemoglobin 80 per cent leukocytes 18 500 with 36 per cent neutrophils and 64 per cent lymphocyte Reexamination showed leukocytes 18 000 with 30 per cent neutrophils and 70 per cent lymphocytes Blood culture was sterile Hemorrhage from the nose and mouth and into the skin continued and she died in August 1928 aged 40 Autopsy was not done but close observation throughout her illness permitted no diagnosis other than lymphatic leukemia

(3) Am J M S 03 3 M h, 194

of symptoms and admission in 52 cases was 10½ months

Although Hodgkin s disease is usually generalized with widespread involvement of the reticulo endothelial system definite areas of localization are observed clinically The early stages are characterized by unilateral lymphadenopathy The lymph nodes of the neck were involved first in 36 cases in 7 of which involvement was bilateral Mediastinal involvement was present in 30 cases The stomach and regional lymph nodes were involved in two cases these were first thought to be cases of inoperable carcinoma until biopsy revealed Hodgkin s disease Splenomegaly occurred in 33 3 per cent hepatomegaly in 37 per cent There was clinical icterus in two cases Cutaneous involvement was proved histologically in two cases and in four there was roentgen evidence of osseous involvement

Opinions regarding the blood picture in *Hodgkin s* disease differ widely Steadily progressive anemia of the hypochromic type is usually found In this series 32 patients had a leukocyte count above 8 000 The two highest leukocyte counts were 68 300 and 54 000 with polymorphonuclears predominant eosinophils were not present in the blood smear in the first instance and were 2 per cent in the second In both cases the leukocytosis was accompanied by rather severe secondary anemia Both patients had superficial lymph node enlargement plus bony involvement The leukocyte count of one patient receiving no treatment was 2 600 In five patients receiving roentgen therapy previously normal leukocyte counts were depressed below 4 000 The leukocyte counts of the rest of the patients were within normal range

Eosinophilia has long been stressed as a characteristic finding In this series there was eosinophilia (5 per cent or more) in 20 3 per cent of cases The highest was 25 per cent occurring in a patient with Hodgkin s disease of the skin associated with superficial lymph node disease

Of the 54 patients in this series, all but 5 whose disease was in an early stage were pyrexic A continued or swinging pyrexia with temperatures of 100 to 104 F was

affecting twice as many males as females and characterized by anemia fever a tendency to uncontrollable hemorrhage and susceptibility to infection Duration is usually less than four months and usually the course is either uninfluenced or adversely affected by roentgen therapy

Lymphosarcoma cell leukemia is a distinct morphologic and clinical entity characterized by presence of lymphosarcoma cells in the blood stream Blood films made on cover slips surfaced with brilliant cresyl blue and stained after drying with Wright s stain show according to Isaacs that the lymphosarcoma cell possesses certain differentiating features the most marked being the peculiar characteristics of the nucleolus This is usually eccentrically placed single very rarely multiple the nucleolus stands out as a sky blue round area surrounded by a deep blue black rim of chromatin which is piled up around it In the true immature lymphocyte or lymphoblast under these conditions the nucleolus appears as a light blue hole or area in the chromatin structure without the heavily staining rim The nucleoli are more likely to be multiple in the immature lymphocytes or lymphoblasts than in the lymphosarcoma cell

Males are predominantly affected and the disease may occur at any age After development of a leukemic blood picture the course is usually rapid but in some cases cautious roentgen therapy is noticeably beneficial

Lymphocytic leukemia affects more males than females and occurs almost exclusively in middle and later years of life Its course may be relatively benign and is usually favorably influenced by roentgen therapy

The prognosis and therapeutic indications cannot safely be based solely on morphologic characteristics of the affected cells but the histologic condition of the blood and the blood forming organs as a whole considered in conjunction with the clinical features provides a basis for a plan of treatment and a reasonably accurate prediction of the course

CASE 2 —A sister developed general weakness and cervical adenopathy in late 1934, at the age of 55 In February 1935 blood study revealed erythrocytes, 3 950 000 hemoglobin, 68 per cent leukocytes, 36 500, with 20 per cent neutrophils and 80 per cent lymphocytes The course was progressive with increasing loss of weight and strength and development of generalized adenopathy Blood studies in March 1936, revealed erythrocytes 3,900 000 hemoglobin 76 per cent (Sahli) leukocytes 153 000 with 2 per cent neutrophils 95 per cent lymphocytes and 3 per cent pathologic lymphocytes Five days later there were 190,000 leukocytes with 1 per cent neutrophils and 99 per cent lymphocytes Chronic lymphatic leukemia was diagnosed Roentgen therapy was given but she died in March 1936 aged 56 Autopsy was not done

CASE 3 — A sister was first seen in August, 1939 at the age of 55 with symptoms of one year s duration consisting of fatigue weight loss and ecchymoses Temperature was 99 6 F pulse 120 blood pressure 170/100 One small hemorrhage was present in the right fundus oculi and there were several large ecchymoses on the lower extremities but no fine petechiae No glands were palpable The spleen was felt at the level of the umbilicus Blood study showed erythrocytes, 2 570 000 hemoglobin 68 per cent (Haden Hausser) leukocytes 162 000 with 57 per cent neutrophil , 2 per cent lymphocytes 30 per cent myelocytes and 8 5 per cent myeloblasts Ten days after roentgen therapy to the spleen the leukocyte count was 11 500 with 60 per cent neutrophils, 19 per cent lymphocytes 2 per cent monocytes 10 per cent eosinophils, 8 per cent basophils and 1 per cent myelocytes Roentgen therapy has been given following relapses on three subsequent occasions When last examined in May 1941, she felt well generally the spleen was not palpable there was no adenopathy and the blood count showed 6 650 leukocytes with a practically normal differential ratio and no immature cells Chronic myeloid leukemia was diagnosed

Lymphogenous (Lymphatic) Leukemia Frank H Bethell[4] (Univ of Michigan) analyzed 190 cases of lymphogenous leukemia subdivided into cases of lymphoblastic lymphosarcoma cell and lymphocytic leukemia on the basis of the morphologic characteristics of the pathologic lymph cells in the circulating blood with respect to age and sex incidence symptoms duration of life and therapeutic response

Lymphoblastic leukemia is a disease of childhood

(4) J A M A 118 95 99 Jan 10 1942

tion After the twenty fourth hour lower levels were observed which gradually tapered off to the near zero level on the eighth day The maximum level in the red blood cells usually occurred 6 24 hours after administration No correlation could be established between the radiophosphorus concentration and the degree of anemia or amount of hemoglobin In most cases regardless of the acuteness or chronicity of the leukemic process the radiophosphorus levels of the white blood cells rose during the first 48 hours and then either continued to rise slowly or maintained a high plateau for days The levels in the white blood cells of normal persons were considerably lower during the first 48 hours than those of leukemic patients i e normal white blood cells retain less radiophosphorus than leukemic cells This may be due among other reasons to a more rapid rate of phosphorus metabolism or of reproduction of leukemic cells

The normal individuals after oral administration excreted in urine and feces a greater percentage of administered radiophosphorus than did the patients After the forty eighth hour more radiophosphorus was excreted in the urine than in the feces of the normal individuals and there is no reason to assume that this does not continue until all of the radiophosphorus absorbed by the body is eventually excreted The patients apparently excreted the radiophosphorus more slowly

Absorption rates following intravenous administration of radiophosphorus to 2 normal individuals and 16 patients were not identical with those noted following oral administration Plasma radiophosphorus levels during the first few hours after administration were slightly higher and the radiophosphorus content in the peripheral red blood cells rose more rapidly to considerably higher levels The leukemic white blood cells took up more quickly and retained greater amounts of radiophosphorus than the normal white blood cells Leukocytes of normal individuals retained only slightly greater amounts of radiophosphorus when it was administered intravenously

Treatment of Leukemia by Radioactive Phosphorus Shields Warren[5] (Harvard Univ) reports four cases of acute or subacute leukemia treated with radiophosphorus injected intravenously in the form of dibasic sodium phosphate Dosage was 1 4 m eq Some improvement was seen in two patients as evidenced by their general condition leukocyte count and condition of bone marrow These patients are moderately active Two patients showed no significant response beyond minor changes in the white cell count both are dead This therapy is experimental and does not displace present methods of radiation for treatment of leukemia

Clinical Studies with the Aid of Radiophosphorus IV Retention in Blood, the Excretion and the Therapeutic Effect of Radiophosphorus on Patients with Leukemia L A Erf I W Tuttle and J H Lawrence[6] (Univ of California) point out that radiophosphorus has been used therapeutically during the past three years in all types of leukemia with encouraging results Its principal advantages are ease of administration therapeutic effectiveness and absence of nausea, radiation sickness and other symptoms following administration Since the half life of radiophosphorus is but 14 3 days there is no danger of cumulative radiation effects similar to those produced by radium or thorium which have half lives of hundreds of years Furthermore 25 50 per cent of a dose of radiophosphorus is excreted by normal individuals during the six days after administration and 1 2 per cent daily thereafter At that rate and considering the constant rate of decay about 15 per cent of a dose would be retained at the end of two weeks Six to eight weeks after a single administration only insignificant amounts of radiation are found in any tissue including osseous tissues

The absorption rate of radiophosphorus administered orally was measured in 2 normal persons and 18 patients In all the radiophosphorus content in the plasma was greatest before the second hour after administra

(5) New England J Med 3 751 754 No 7 1940
(6) Ann Int Med 15 487 43 Sept [illegible]

was quite similar in both of the groups of patients

Autopsy findings reveal that the amounts of radio phosphorus so far administered have not morphologically altered normal tissues

Leukemoid Reaction (Hyperleukocytosis) in Malignancy The leukemoid reaction described in various conditions has been of two distinct varieties In one the total white cell count has been either normal or slightly increased but smears of the peripheral blood disclosed large numbers of myelocytes and myeloblasts in the other type the total count has been extremely elevated with or without marked shift to the left of the polymorphonuclear cells The bone marrow has in all instances of both types shown absence of a true leukemia hence the designation leukemoid

Krumbhaar reported 10 cases including one of carcinoma of the breast in which the white cell count rose to 102 000 with 92 per cent segmented polymorphonuclears and only 4 per cent myelocytes Sonnenfeld reviewed the literature up to 1929 and found 12 cases of various types of malignancy associated with a leukemoid blood picture in many of which there was evidence of bone metastasis In these cases the white cell counts ranged from 15 000 to 140 000 with immature cells varying from 20 to 30 per cent myelocytes He added two cases The first was one of carcinoma of the liver in a man 61 whose white cell count rose to 104 000 with 30 per cent mature eosinophils many promyelocytes being present The second was in a man 60 with gastric carcinoma with 125 000 leukocytes 39 per cent metamyelocytes and 7 per cent myelocytes In neither case were bone metastases found Leo M Meyer and Saul D Rotter[7] (Kings County Hosp Brooklyn) report two cases of carcinoma of the stomach with marked quantitative changes in the blood the white cells being almost entirely of the mature type

Case 1—In a man 66 with gastric carcinoma blood studies revealed hemoglobin 30 per cent erythrocytes 1 580 000 leukocytes 110 000 with 94 per cent polymorpho

(7) Am J Cl P th 12 18 Ap l 194

than when given orally while the leukemic cells retained considerably more following intravenous administration Small and nearly equal amounts of radiophosphorus were excreted in the feces of both normal individuals and patients But the former excreted more radiophosphorus in the urine during the first 48 hours than was excreted by the latter group during the same period The normal individuals excreted more radiophosphorus in the urine following its intravenous than its oral administration but this was not true for the patients After the 48 hour period following administration, both groups excreted in the urine and feces similar amounts of radiophosphorus and this undoubtedly continued until all of the radiophosphorus absorbed was ultimately excreted

A summary of results obtained in two large groups of patients are given in the table

RESULTS IN CASES OF MYELOID AND LYMPHOID LEUKEMIA

Type of Disease	Myeloid Leukemia		Lymphoid Leukemia	
	Acut	Chro	Acute	Chronic
No of cases	8	38	16	25
No of partial remissions	0	11	1	8
No of complete remissions	0	5	1	1
No dead	8	21	15	13

Two patients have had essentially complete remissions for nearly two years Of 10 patients with chronic lymphoid and 12 with chronic myeloid leukemia who had had no therapy previous to radiophosphorus 4 in each group died (3 in the former group and 1 in the latter were moribund when radiophosphorus was first administered) while the other 14 had either partial or complete remissions for 6 to 12 months Results in those patients who had had x radiation prior to administration of radiophosphorus are not so encouraging and the authors accordingly feel that x radiation reduces the effectiveness of radiophosphorus since duration of the disease processes previous to administration of radiophosphorus

Of these, marked leukocytosis is perhaps the least common In these cases the blood shows a truly leukemoid type of response W Laurence Whittemore and Melvin H Stich[8] (City Hosp Welfare Island New York City) report a case

Woman 34 admitted in diabetic coma was started on the routine intensive diabetic acidosis regime The second day temperature rose suddenly to 101 F and examination revealed lobar pneumonia throughout the right lung Blood studies at this time showed leukocytes 10 800 with a differential count of 2 per cent metagranulocytes 10 per cent rhabdocytes 79 per cent polymorphonuclear lobocyte 8 per cent lymphocytes and 1 per cent monocytes erythrocytes 4 400 000 hemoglobin 85 per cent (Sahli) thrombocytes adequate on smear

Therapy was begun with sulfathiazole with initial dose 2 Gm followed by 1 Gm every four hours Oxygen was also administered Temperature continued to rise and three days later was 103 8 F The patient was cyanotic even with oxygen and was completely disorientated although the diabetic condition was well under control Sulfadiazine 3 Gm initially followed by 1 Gm every four hours was then substituted for sulfathiazole There were 14,200 leukocytes at this time A total of 37 Gm sulfadiazine was given with manifest improvement

The day following withdrawal of sulfadiazine the patient appeared extremely pale and blood studies showed leukocytes 85 000 hemoglobin 34 per cent Several hours later the leukocytes numbered 90 400 Differential count showed 8 per cent promyelocytes 8 per cent myelocytes 9 per cent metamyelocytes 8 per cent rhabdocytes 30 per cent polymorphonuclear lobocytes 8 per cent lymphocytes and 28 per cent nucleated red blood cells Platelets were adequate on smear

A transfusion of 500 cc blood was given and repeated two days later The second day following discovery of the leukemoid reaction blood studies showed leukocytes 9 800 with differential count of 4 per cent metamyelocytes 16 per cent rhabdocytes 48 per cent polymorphonuclear lobocytes and 32 per cent lymphocytes hemoglobin was 44 per cent Hemoglobin rose to 55 and 66 per cent two and five days later respectively Color improved and temperature remained normal The last blood study approximately one month later, showed leukocytes 9 000 with differential count of 68 per cent polymorphonuclear lobocytes 6 per cent rhabdocyte and 26 per cent lymphocytes hemoglobin was 80 per cent.

(8) New York State J Med 42 1 49 1250 July 1 194

nuclears 4 per cent lymphocytes and 2 per cent myelocytes Numerous normoblasts were seen in the smears Subsequent blood counts showed persistent secondary anemia Total leukocyte counts ranged between 72 000 and 110 000 and total polymorphonuclear counts between 91 and 98 per cent Myelocytes were no longer found Course was progressively down hill Autopsy revealed adenocarcinoma of the stomach with localized peritonitis Marrow from sternum and vertebra showed marked hyperplasia of the myeloid elements with evidence of maturation to normal polymorphonuclear cells Frequent megakaryocytes were seen The spleen showed marked reduction in number and size of malpighian corpuscles, the stroma of the pulp was overwhelmed with large numbers of mature polymorphonuclears

CASE 2 —*In a woman 42 with carcinoma of the stomach*, blood studies showed erythrocytes 4 125 000, hemoglobin 75 per cent leukocytes 66 250, with 78 per cent segmented polymorphonuclears 11 per cent band forms, 9 per cent myelocytes and 2 per cent lymphocytes Study 10 days later showed erythrocytes 3 860 000 hemoglobin, 70 per cent leukocytes 128 000 with 58 per cent lobed neutrophils 23 per cent band forms 13 per cent myelocytes and 2 per cent myeloblasts Autopsy revealed anaplastic carcinoma of the stomach with metastases to liver, spleen and abdominal lymph nodes Section of ribs sternum vertebrae pelvis and femur showed no further evidence of metastases The bone marrow consisted of densely packed polymorphonuclear cells, many of which were younger forms Myelocytes were numerous and blast forms were also seen The splenic sinuses were packed with young and old polymorphonuclear cells, with compression and atrophy of the follicles

Leukemoid Reaction to Sulfadiazine Among the more serious toxic manifestations occurring during sulfonamide drug therapy are those involving the hemopoietic system The various reported toxic blood pictures may be classified as follows

A Involving the leukocyte series
   1 Leukopenia
   2 Agranulocytosis
   3 Marked leukocytosis
B Involving the erythrocyte series
   1 Mild to moderate anemia
   2 Acute hemolytic anemia
C Involving the thrombocyte series
   1 Thrombocytopenia
D Combinations

close study of the time factor involved in the fall of thrombocytes was made possible by experimental administration of sedormid to these patients It was found that there is a rapid disappearance of thrombocytes from the blood in especially hypersensitive patients as early as 30 60 minutes after ingestion of the test dose (½ tablet) of sedormid This could only be explained by a destruction of platelets already present in the circulation and not merely by inhibition of platelet production in the bone marrow Two transfusions of blood withdrawn from a patient with typical sedormid thrombocytopenia during the height of thrombocytopenic reaction given to a nonsensitized patient failed to produce a reduction of thrombocytes in the latter s blood indicating that the serum of the donor contained no platelet lysins Moreover the negative results of experimental administration of sedormid to the recipient the day following the transfusion testified against passive transferability of sedormid hypersensitivity

It is concluded that in hypersensitive individuals sedormid by an unexplained mechanism causes damage to the thrombocytes in the blood and a transitory impairment of megakaryocyte maturation in the bone marrow analogous to the damage to granulocytes in blood and marrow in agranulocytosis The hypersensitivity to sedormid and similar substances is probably a central rather than peripheral phenomenon due to sensitization of certain nerve centers which control the entire platelet apparatus

Menorrhagia as Primary Factor in Various Blood Dyscrasias Various blood dyscrasias such as purpura haemorrhagica aplastic anemia and leukemia ordinarily have easily identifiable diagnostic characteristics Occasionally however the presenting and only symptom is menorrhagia In a review of 108 cases of purpura haemorrhagica aplastic anemia and leukemia C I Buxton[5] (Columbia Univ) found that 10 of the patients presented themselves for treatment with a

(5) Am J Ob t & Gy e 4 50 505 Septembe 1941

The toxic effect of sulfadiazine was evident in both leukocytic and erythrocytic series the effects on the latter apparently being the more serious and more lasting The prompt response of the leukocyte series after withdrawal of the drug is remarkable the white blood cell count being within normal limits two days after discovery of the leukemoid reaction

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PURPURA

The articles in this section discuss various aspects of purpura whether associated with platelet lack or with capillary fragility — Eds

Study of Sedormid Thrombocytopenia by Means of Sternal Punctures, Load Tests and Transfusions in 10 patients is reported by Sven Moeschlin[4] (Univ of Zurich) Repeated sternal punctures were possible in two of the patients Examination of the sternal marrow smears revealed that within the first 24 hours of thrombopenia there was no significant deviation from normal in regard to number and morphology of megakaryocytes On subsequent days there was a slight increase in immature forms such as promegakaryocytes and half matured forms with basophilic granules Megakaryoblast and promegakaryocyte mitoses as reported by others were not encountered in this series Aside from a slight increase in erythroblasts as result of repeated hemorrhages the bone marrow remained uninfluenced With return of the thrombocytic level to normal the appearance of megakaryocytes in the bone marrow likewise became normal

Provided the drug was withdrawn there began usually the third day following the acute thrombocytopenia, a steady and progressive rise in thrombocytes reaching a normal (sometimes above normal) level in five to seven days During the regenerative phase giant platelets with unusual amounts of basophilic granules and vacuolized forms appeared in the circulating blood A

(4) Schweiz med Wchnschr 1191 4 J 31 1943

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(5) Am. J Ob t & Gynec 4 0 505 September 1941

chief complaint of menorrhagia In many other cases this symptom occurred as one of the incidental factors in a condition already diagnosed yet in this series nearly 10 per cent of the patients with blood dyscrasias were first seen in a gynecologic clinic or were first treated for their gynecologic complaint In seven of these cases subsequent diagnosis was purpura haemorrhagica, in two aplastic anemia and in one acute lymphatic leukemia Although the total number of cases of uterine bleeding with occult blood dyscrasias must be relatively small it is significant enough to warrant complete blood studies on every unexplained case of menorrhagia

[Other specialists who sometimes have the first opportunity to make the diagnosis of a blood dyscrasia because of its local manifestations are dentists otolaryngologists and dermatologists — Eds]

Effect of Transfusion on Capillary Resistance Harold Scarborough[6] (Royal Infirmary Edinburgh) reports that capillary resistance is increased markedly and immediately (within 24 hours) following transfusion of blood and/or plasma This effect has been obtained with fresh blood with blood stored for 7 days with whole plasma stored for 10 days and with plasma saline (50 50 mixture) stored for 7 months but not with 5 per cent glucose saline The increase in capillary resistance (negative pressure method) can occur in the absence of any clinical improvement In two of the four cases studied it was maintained for at least 10 days but in the other two a more temporary effect lasting 4 5 days was obtained The increase in capillary resistance is maintained longest in an area lying across the mid line of the anterior aspect of the arm 2 cm proximal to the carpal flexure as contrasted to areas 4 cm below the elbow flexure The increase may occur in subjects exhibiting very different levels of capillary resistance during the preliminary control period These results are presumed to indicate a direct effect of blood and plasma transfusion on the capillary walls themselves

(6) Edinburgh M J 48 55 560 Aug 1, 1941

HEMOPHILIA AND OTHER VARIETIES OF DEFECTIVE BLOOD COAGULATION

The first article by Howell serves to orient the reader to the present status of problems in the field of defective blood coagulation. Other articles are concerned with hemophilia and naturally occurring prothrombin deficiency. The final three articles discuss the properties and use of a synthetic agent dicoumarin which produces in vivo but not in vitro a decrease in prothrombin content of the blood. This property is of practical interest and importance in the prevention of thromboses of the veins.—Eds

Recent Advances in Problem of Blood Coagulation Applicable to Medicine are discussed by William H Howell[7] (Baltimore). The most significant recent contribution to the subject of blood coagulation is the discovery of vitamin K which is essential to the formation of prothrombin. This discovery coincided with work on the effect of jaundice and liver injuries on the concentration of prothrombin in the blood. The natural vitamin K is believed to be a methyl phytyl naphthoquinone, and a number of related compounds have been synthesized which show to varying degrees a similar activity in promoting prothrombin formation. It has been shown that presence of bile is necessary for adequate absorption of the vitamin and that its activity after absorption is exerted in the liver. Older work indicates that prothrombin may be produced also in the bone marrow but the consensus is that this function is performed mainly if not entirely by the liver. Structural injury to this organ is followed by reduced prothrombin output. Prothrombin determination tests have shown that certain well known hemorrhagic conditions are due to a fall in concentration of this factor; a reduction to 10 to 20 per cent of normal is likely to be followed by hemorrhagic symptoms. Such a reduction may occur under conditions which affect the supply, absorption or utilization of the vitamin. With obstructive jaundice and biliary fistulas there is interference

(7) J A M A 117 1059 1062 Sept 7 1941

with absorption owing to lack of bile in the intestine *and it seems probable that other diseases which affect* intestinal functions such as ulcerative colitis or sprue may have a similar action In cases in which liver function is normal administration of vitamin K suffices to restore prothrombin to the blood and arrest bleeding

No cases of prothrombinopenia in the adult have been reported as due to dietary deficiency of the vitamin The explanation given is that an intrinsic source of vitamin is furnished by the bacterial flora of the intestine which is sufficient to give an adequate supply when *the diet itself is deficient or lacking in vitamin K In* the new born infant however there occurs in the first 24 hours a fall in prothrombin level which is considered the basic cause of hemorrhagic disease of the new born In a few days the prothrombin concentration normally rises spontaneously to or toward normal probably because of prompt establishment of intestinal bacterial flora If return to normal is delayed hemorrhagic conditions may develop but these are readily obviated by vitamin K administration Similarly administration of vitamin K to the mother before delivery prevents the postnatal drop in prothrombin in the infant s blood and thus wards off the danger of hemorrhage

When the vitamin K supply is adequate and absorption is normal prothrombin deficiency may occur if its proper utilization is retarded or prevented by serious structural damage of the liver Under such conditions even massive doses of vitamin K may be without effect on the prothrombin level

Another important clinical application of coagulation studies is found in the attempts to use heparin to control thrombosis and embolism under pathologic conditions and after surgical operations It has been shown experimentally that intravascular injections of heparin serve to prevent thrombus formation after mechanical or chemical injury to the lining of the blood vessels or heart and *that arterial anastomoses, embolectomies and* transplantations of organs may be performed after

heparinization with less danger of thrombosis than in similar operations without heparin Clinically the most impressive results reported concern the effect of heparin in preventing postoperative thrombosis and embolism

Clinical control of the hemorrhagic condition due to hemophilia has made less progress In hemophilic blood all coagulation factors with the exception of thrombo plastin are present in normal concentration hence the efficacy of blood transfusion in the control of hemophilic bleeding Since tissue extracts added to normal or hemophilic blood in vitro hasten its coagulation it was to be expected that attempts would be made to control hemophilic bleeding and hemorrhage from other causes by intravenous injection of such extracts Numerous ex periments of this kind have been made but results have not been wholly successful partly perhaps because in some cases the hemorrhagic condition was not due to thromboplastin deficiency and partly because of the danger of intravascular clotting or serious protein re actions. In most cases relatively crude extracts have been used which contained other substances in addition to thromboplastin itself A globulin fraction of normal plasma which may be given intravenously or intra muscularly reduces the coagulation time for several hours [This is the basis of the well known effect of repeated small transfusions of blood which remain the best means of shortening the coagulation time in hemo philia —Eds] It remains possible that if thrombo plastin were isolated in pure form it could be used intravascularly in graded dosage in hemophilia to restore the normal blood thromboplastin level

Effect of Foreign Surfaces on Blood Coagulation Observations by Eugene L Lozner and F H L Taylor[8] (Harvard Univ) show that the effect of foreign sur faces on blood coagulation is essentially independent of the intact platelet The site of action of such sur faces depends on a factor present in normal cell free plasma independent of prothrombin and fibrinogen

(8) J Clin. I tig t 21 41 4 M h 194

associated with the euglobulin fraction of the proteins and concerned with the clot promoting activity of plasma for hemophilic blood That this globulin substance might be derived from damaged platelets *cannot* be excluded by the present observations However, it is present in cell free plasma and foreign surfaces have *entirely similar* effects on platelet free and platelet *rich* plasma The authors data clearly indicate that the effect of foreign surfaces is not accompanied by any increased lysis of the platelets *prior to clot formation,* as heretofore assumed

Exposure to a glass surface had more effect in 'activating' the factor involved than did surfaces of paraffin collodion or lusteroid The term 'activating' is applied to the effect of glass rather than explaining the effect *of collodion paraffin* and lusteroid as due to an 'inhibition' of the plasma factor involved because plasma placed first in glass vessels and then transferred to tubes *of the other foreign surfaces* behaves *as plasma exposed* to glass alone

The exact mechanism of the foreign surface effect can only be hypothecated A *possible hint of the type* of reaction involved lies in the work of Gortner and Briggs who showed by streaming potential methods that *the charge on a glass surface* in contact with water is considerably greater than that on a paraffin surface These authors have also suggested that a positively *charged* substance in blood may be adsorbed by a negative surface such as that presented by a glass interface It is therefore possible that the foreign surface effect

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coagulation time in hemophiliacs reveals marked similarity in the extent of reduction and duration of the effect The effect produced has been found to be practically maximal 15 minutes after injection To obtain maximum thromboplastic potency the plasma must be lyophilized within the first few hours after removal from the donor Thromboplastic activity of lyophile plasma is maintained for at least three months when the dried plasma is kept at 5 C Such plasma can be given safely irrespective of the blood type of recipient or donor The average dose of plasma given at one time is 125 150 cc This dosage reduces coagulation time to 15 to 25 minutes for approximately 20 hours after injection whereupon a gradual rise in coagulation time to about 40 minutes is achieved 50 hours after injection

Five cases studied demonstrate the effectiveness of this plasma in the management of hemarthroses hematuria and tooth extractions in patients with hemophilia One almost totally disabled patient to whom weekly injections have been given has been rehabilitated sufficiently so that he can do light steady work

Thrombic Activity of a Globulin Fraction Derived from Rabbit Plasma The observation of Parfentjev that rabbit plasma contains a substance or physiologic activity capable of converting fibrinogen to fibrin has been confirmed by F H L Taylor Eugene L Lozner and Margaret A Adams[1] (Harvard Univ) This material is apparently a pseudoglobulin which possesses thrombic activity i e it converted fibrinogen to fibrin without calcium prothrombin or thromboplastin When rabbit thrombin containing 0 03 mg nitrogen was added to 1 cc citrated human plasma total conversion of fibrinogen to 2 25 mg fibrin resulted It may be differentiated from thromboplastin by its manner of preparation and its independence of calcium ion concentration in its action on fibrinogen There is however no evidence that this thrombic activity is not due to changes in plasma proteins incident to the salting out pro

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Management of Hemophilia with lyophile human plasma given intravenously is discussed by John B Johnson[9] (Univ of Rochester) Lyophile plasma affects the coagulation time in hemophilia in a manner similar to that of fresh whole blood Comparison of the effect of fresh citrated blood and that of dried plasma on the

rabbit thrombin was complete and immediate i e as soon as the dressing pack or gauze bite was applied to the bleeding surface, arrest of hemorrhage immediately occurred Prior to application of rabbit thrombin hemorrhage had occurred for varying periods In 9 of the 11 patients hemorrhage had not been controlled by various hemostatics including pressure bandaging and application or tamponage with adrenalin ferric subsulfate solution and animal muscle In one patient with hypertension and epistaxis bleeding had persisted for 14 days prior to rabbit thrombin therapy despite all these measures and four blood transfusions

In the one patient in whom hemostasis on the first application of rabbit thrombin was only partial the diagnosis was symptomatic thrombocytopenic purpura associated with aplastic anemia Two subsequent applications on following days produced complete and immediate hemostasis

No toxic effects from application of rabbit thrombin were observed in any of the normal subjects or patients no matter in what form it was applied It is important however that the material be used cautiously for parenteral administration may result in generalized thrombosis

[*The next three articles discuss certain aspects of prothrombin deficiency* —Eds]

Idiopathic Hypoprothrombinemia—An Apparently Unrecorded Condition Jonathan E Rhoads and Thomas Fitz Hugh Jr[3] (Univ of Pennsylvania) report the case of a supposed hemophiliac in whom a prothrombin deficiency was subsequently found

Youth 18 presented a hemorrhagic diathesis extending over most of his life span Up to his death on Dec 15 1940 he had been hospitalized 26 times because of hemarthroses hematomas following contusions and a tendency toward uncontrollable bleeding from wounds Family history was negative for any abnormal hemorrhagic tendency Initial observation on Nov 9 1929 when the patient was 6 revealed a venous coagulation time of 41 minutes and a diagnosis of

(3) Am J M S 0 662 670 No mb 1941

cedures involved in its preparation Solutions of rabbit thrombin are thermolabile but are reasonably stable for months at room temperature Complete stability was obtained when the preparations were lyophilized or precipitated with acetone and dried in vacuo Gauze saturated with solution of rabbit thrombin can be dried under reduced pressure without significant loss of activity

Use of Rabbit Thrombin as Local Hemostatic Eugene L Lozner Harriet MacDonald Maxwell Finland and F H L Taylor (Harvard Univ) report on a controlled study of hemostasis following standard trauma in normal subjects and on the use of rabbit thrombin in control of bleeding from small wounds in patients with and without hemorrhagic diseases

The most effective manner of application of rabbit thrombin in the control of bleeding from standard trauma in normal subjects was found to be 'dry application wherein a square of saline moistened filter paper was applied to the wound and sprinkled with a small amount of dry rabbit thrombin The next most effective procedure consisted of spraying the wound with dry powdered rabbit thrombin Least effective were wet applications and wet sprays of solutions of rabbit thrombin

Observations were conducted on 11 patients who were bleeding from small wounds Nine of these had hemorrhagic diatheses four hemophilia three symptomatic thrombocytopenic purpura one hypoprothrombinemia and one hereditary thrombasthenia The other two had hypertension with epistaxis Dry powdered rabbit thrombin was usually used and the technic of application consisted essentially of impregnating with the dry powder a dressing pack or gauze bite which has been dampened with sterile saline This impregnation is carried out so as to allow the dry powder to come into immediate contact with the bleeding surface

With only one exception the hemostasis produced by

(1) Am J M S 0 593 598 O t ber 1941

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(3) Am. J [illegible] 6?2 6 0 November 1941

hemophilia was made Venous coagulation time was prolonged, except on two occasions, and because it was not rechecked at these times it is doubtful if these readings are significant Clot retraction was regarded as normal on Aug 6, 1931, and Mar 14 1932 It was retarded Feb 16 1934, and was noted as poor Oct 18 1938 and Mar 18, 1940 The platelet count was usually normal and was never low enough to account for the hemorrhagic diathesis Serum calcium concentration was 9 8 mg per cent on May 2, 1938, and 10 mg per cent on Mar 19 1940 *The prothrombin time* (Quick) was uniformly prolonged values of 70 to 107 seconds being obtained from Mar 30 1938 to Sept 12 1940 *Fibrinogen concentration on Mar 26 1940 was 315 mg per* cent There was no indication of excess antithrombin or antiprothrombin Neither was there an excess of heparin to cause *the delayed clotting The possibility* that the prolonged prothrombin time was due to a delay in the conversion of prothrombin to thrombin was also excluded An additional contributory factor to the hemorrhagic diathesis was an abnormality of the fibrinogen evidenced by an unusual resistance to the action of thrombin

Clinical study revealed neither K avitaminosis nor a conditioned deficiency of vitamin K due to lack of bile salts Because *hypoprothrombinemia due to liver damage* is *not* very responsive to treatment with vitamin K by either oral or parenteral routes it was considered possible that this patient had hepatic damage or perhaps hepatic hypoplasia Liver function tests however showed no evidence of hepatic damage and at autopsy no gross abnormality of the liver was discernible and the microscopic changes were much less than have been observed previously in patients with hypoprothrombinemia *due to liver damage*

Response to Vitamin K as an indication of liver function is discussed by Robert Kark and Alexander W Souter[4] (Harvard Univ) They studied 57 cases among which were cases of portal and biliary cirrhosis catarrhal jaundice toxic or infectious hepatitis and some with intense jaundice difficult of diagnosis The initial level of blood prothrombin before parenteral administration of vitamin K and the character and degree of response *following its administration* were *used as criteria* of diagnosis Analysis of data showed that these 57 cases with clinically evident liver disease could be placed in five subdivisions

(4) Lan et 2 693 69

Group 1 constituted cases in which the lowered blood prothrombin content rapidly (24 48 hours) returned to within 90 100 per cent of normal after vitamin K therapy When intense jaundice and significant hypoprothrombinemia are present and when diagnosis is doubtful a response of this type indicates the probability of obstructive jaundice The good response to therapy implies that no gross parenchymatous liver disease exists and that the low prothrombin level results from vitamin K deficiency due to absence of bile salts in the bowel

Group 2 included cases in which the lowered blood prothrombin level rose somewhat but remained fixed at a subnormal level despite repeated administration of vitamin K This response in jaundiced patients indicates acute or subacute parenchymatous liver damage of moderate and variable degree In such patients swelling of hepatic cells exerts pressure on the intrahepatic ducts and, following development of intrabiliary obstructive jaundice vitamin K is not absorbed from the bowel Therapy with vitamin K and bile salts is effective but although restoration of blood prothrombin level is rapid it is incomplete because of disturbed prothrombin production in the liver

In group 3 the blood prothrombin level rose gradually with treatment coincident with clinical improvement Jaundice may or may not develop in patients exhibiting such response Fever is usually present and may be associated with an acute septic process involving especially the biliary tree The moderately lowered blood prothrombin content does not respond to vitamin K therapy or exhibits only slight immediate response This is because in most of these patients there is no true dietary lack of vitamin K but there is inability of the liver to utilize absorbed vitamin K Hence the low prothrombin level With clinical improvement either through subsidence of an acute infectious process or because the initial liver disease clears up the prothrombin level eventually reaches normal This group includes patients with infective cholangitis catarrhal jaundice

acute and toxic hepatosis patients undergoing heat therapy and patients with obstructive jaundice complicated by an associated infection

Patients in group 4 had a prothrombin level fluctuating at a subnormal level (40 60 per cent) but above the threshold for hemorrhage irrespective of therapy These patients present chronic liver disease usually unassociated with jaundice There is neither dietary deficiency of vitamin K nor evidence of malabsorption but the liver is unable to produce sufficient prothrombin to maintain normal levels These patients include those with hepatic cirrhosis and those with Banti s syndrome

Group 5 was made up of cases in which the lowered blood prothrombin level dropped despite therapy and remained below the level for hemorrhage Such patients have severe and extensive liver damage Clinically they appear ill and present hemorrhagic manifestations The blood prothrombin concentration is in the 'hemorrhagic zone' and often continues to drop despite therapy The severely damaged liver is incapable of producing prothrombin Prognosis is grave Autopsy will reveal acute hepatitis or generalized malignant infiltration of the liver

The Chemistry of Vitamin K is discussed by Louis F Fieser* (Harvard Univ) The known list of natural antihemorrhagic factors includes only vitamin K_1 from alfalfa and vitamin K_2 from putrefied fish meal Vitamin K_1 is 2 methyl 3 phytyl 1 4 naphthoquinone and vitamin K_2 probably is 2 methyl 3 difarnesyl 1 4 naphthoquinone The two substances are closely related in chemical structure, for they have the identical quinone nucleus and each possesses a long side chain made up of the same branched 5 carbon units They constitute two members

phytol is identical in every respect with natural vitamin K_1 isolated from alfalfa and is available for use

A common misconception is that significant vitamin K activity is exhibited by a large number of simple quinones The list of quinones possessing significant activity i e at least one twenty fifth the activity of vitamin K includes only the actual vitamins and their immediate derivatives 2 methyl 1 4-naphthoquinone which represents a component part of the vitamin K_1 and K_2 molecules and three substances differing from vitamin K_1 only in having in place of the phytyl group the comparable but shorter hydrocarbon substituents farnesyl geranyl and cinnamyl

A high degree of specificity exists in the chemical structures of the natural vitamins Such slight alteration as the addition of two hydrogen atoms which changes the molecular weight only from 451 to 453 results in a four to eightfold loss depending on where the hydrogens are attached while the addition of a CH_3 group which changes the molecular weight by only 3 per cent practically or wholly deactivates the molecule 2 Methyl 1 4-naphthoquinone appears to constitute a single exception for it is a highly active quinone and yet in contrast to the vitamins which have at the three position a side chain which is highly specific with respect to length branching and unsaturation it carries no side chain at all in this position

Chick assay reveals that the synthetic compound possesses three times the potency of vitamin K_1 at least on a weight basis and seemingly therefore is superior to the vitamin factor produced by plant synthesis and provided with the elaborate phytyl chain derived from chlorophyl If the material is administered in such a manner that it finds its way to the gut combination might occur with phytol to give vitamin K_1 while similar substances might well arise from a synthesis occurring in the liver utilizing vitamin A or a carotinoid pigment Such a biosynthesis would entail a three or fourfold increase in molecular weight and would there

fore account for the anomalously high potency of the simple compound on a weight basis in the chick test

Vitamin K_1 is a stable chemically inert substance whereas methylnaphthoquinone is extremely reactive A rapid reaction occurs with sulfhydryl compounds of which thioglycollic acid constitutes a nonbiologic model The crystalline product which results is almost as active in the chick assay as vitamin K_1 it is even more stable than this substance its sodium salt is water soluble and the compound gives promise of being a valuable therapeutic agent The variegated alterations which methylnaphthoquinone may undergo militate however against its therapeutic use The substance evidently can enter into some of the favorable forms of transformation, but the extent to which dissipating side reactions also occur remains in question Consideration should also be given to the possible toxic or otherwise undesirable characteristics which may be associated with conjugates resulting from administered methylnaphthoquinone The fate and action of the administered material appear to be subject to considerable uncertainty and the wide opportunity for transformations of different types would lead one to expect a variability in the response, dependent on the site and mode of administration and the condition of the patient [Not as yet a practical disadvantage clinically —Eds]

The only precaution necessary in using vitamin K_1 is to avoid exposure to light for it is highly photosensitive as is methylnaphthoquinone Fortunately an oxide derivative appears to be relatively insensitive to light and is biologically equivalent to the vitamin It is a nearly colorless oil soluble in alcohol and insoluble in water Considerable interest has centered around the use parenterally of the various water soluble derivatives of methylnaphthohydroquinone However the water insoluble vitamin K_1 or its oxide can be given satisfactorily and effectively in the form of an aqueous emulsion containing as much as 10 mg of the oxide in 10 cc solution With the introduction of vitamin K_1 oxide and development of

a simple technic of preparing emulsions it appears that there is available a practically ideal agent for vitamin K therapy

[The following three articles deal with the therapeutic induction of prothrombin deficiency for the purpose of reducing the coagulating ability of the blood These articles are chiefly concerned with the problem of dosage —Eds]

Studies on the Hemorrhagic Agent 3 3 Methylenebis (4-Hydroxycoumarin) James B Bingham Ovid O Meyer and Frederick J Pohle[6] (Univ of Wisconsin) report studies which indicate that this substance (called dicoumarin) is fully capable of producing prolongation in prothrombin and coagulation time in dogs and humans The substance was isolated by Link and his associates from spoiled sweet clover or silage which causes a hemorrhagic disease in animals It is effective when administered orally or as the disodium salt intravenously The prolongation in prothrombin time is not effective until 24 hours after administration of the material orally and there is a similar but perhaps slightly shorter latent period with intravenous administration For some days varying with the dose the prothrombin time becomes increasingly prolonged and then if no more than a single dose is given gradually returns to normal usually in 5 to 7 days when small doses are given and in 7 to 10 days when large doses are given Whatever the size of the dose the initial latent period always occurred and during the first two days prolongations of prothrombin time were approximately the same Only after this period did the larger doses exhibit the greater depression of prothrombin activity Divided doses given orally were more effective in reducing the prothrombin than was the same quantity given in a single dose this suggested that above a certain level there is some difficulty with absorption of the material

The frequent observation of profound capillary dilatation that follows administration of dicoumarin as demonstrated at autopsy even when only moderate doses are given raises the question of a gross vascular factor in

the hemorrhagic manifestations of sweet clover disease in cattle This factor as a possible contributing mechanism in the production of undesirable bleeding when dicoumarin is used clinically must be borne in mind

The mechanism by which dicoumarin prolongs the prothrombin time and hence the coagulation time, is not known Such an effect does not occur with blood in vitro Vitamin K administration does not counteract the effect of dicoumarin in vivo The possible importance of this substance as a substitute for heparin in prevention of thrombosis is self evident, but is still in the experimental stage Its indiscriminate use may be extremely hazardous even though the therapeutic index appears to be high This material should be used only in selected patients avoiding those with gross hepatic disease and employing only the apparent minimal effective doses

Studies on the Hemorrhagic Agent 3,3' Methylenebis (4 Hydroxycoumarin) Methods of administration and dosage are reported by Ovid O Meyer, James B Bingham and Velma H Axelrod[7] (Univ of Wisconsin) The disodium salt of dicoumarin was given intravenously in varying doses to 27 patients Of these 24 received only one dose and 3 received repeated (2 5) doses Single doses ranged from 0 5 mg per Kg body weight in 2 patients to 6 mg per Kg in 1 15 received 4 mg per Kg The three patients who had repeated doses received 4 mg per Kg each time The smallest doses produced relatively little or no effect the most effective single or repeated dose seemed to be about 4 mg per Kg Patients did not all respond identically to a given dose In all cases without regard to size of dose there was a latent period of about 24 hours before a demonstrable effect occurred After one dose there was a usual period of two to five days before the maximal effect was noted after which there was a gradual return over a three to five day period of the prothrombin time and coagulation time to normal

Dicoumarin was given orally to 46 patients in single

(7) Am J M Sc 04 11 1 July 1942

or repeated doses of 0 75-6 mg per Kg For a time re peated large doses were given orally every three to six days but later an original large dose and subsequent daily small doses were given since the latter method seemed to evoke a more uniform prolongation of pro thrombin time and coagulation time It was found that an initial dose of 5 mg per Kg followed by daily doses of 1 mg per Kg produced a satisfactory response in 5 of 16 patients With an initial dose of 5 mg per Kg followed by 1 5 mg per Kg daily however satisfactory response was noted in 11 of 14 patients This latter dosage is the one now customarily used With the excep tion of a more prolonged latent period the effects of oral administration did not differ significantly from those of intravenous administration In some patients the pro- longation in prothrombin time and coagulation time was greater than desired in such instances the material was withheld for one or more days until there was a trend toward normal

Use of dicoumarin either orally or intravenously has not been attended by any symptoms of toxicity other than hemorrhage Microscopic hematuria occurred in 10 of the 73 patients in 4 patients occult blood by the guaiac test was found in the stool Gross bleeding oc curred in only one case in which curettement of the uterus was performed at the time of dicoumarin admin istration The bleeding was restricted to the operative site

Dicoumarin is potentially capable of inducing unde sirable hemorrhage even in a dosage considered to be within the therapeutic range Its indiscriminate use is extremely hazardous Because of considerable individual variation in response it is imperative that the prothrom bin time and coagulation time be determined daily dur ing dicoumarin administration A coagulation time of approximately 15 20 minutes should be suitable and not too hazardous Prolongation in the prothrombin time to 12½ to 19 seconds (approximately 50 25 per cent of nor mal) is probably reasonably safe At the 19 second level

blood prothrombin is approximately 25 per cent, and lower *levels are not* desirable If the increase of prothrombin time or coagulation *time* becomes too great dicoumarin should be withheld temporarily and, if necessary blood transfusions of 300 to 600 cc should be given *Use of dicoumarin* should be avoided where gross hepatic disease is known to exist

Effect of Synthetic Hemorrhagic Agent, 3 3 Methylenebis (4 Hydroxycoumarin) in Prolonging Coagulation and Prothrombin Time in Man Stuart R Townsend and Edward S Mills[8] (*Montreal Gen'l Hosp*) *gave the compound orally* in six cases *three of which* are reported *here*

CASE 1—Man, 24 admitted with *tuberculous pleurisy* and effusion was given 200 mg dicoumarin compound daily for four consecutive days and on the sixth day 400 mg *There* was little or no change in coagulation or prothrombin *times* before 48 *hours* when both became *prolonged* The highest level was reached in 8 to 10 days *when* coagulation time was 13 minutes and prothrombin time (Quick) 10 seconds *above* normal *levels Ten days after the last* dose the blood had returned to normal levels No other medication was given

CASE 5—*Effects of* small repeated doses were observed in a Chinese *66*, with carcinoma of the cecum Fifty mg thrice daily *for five days* produced *some prolongation of* prothrombin and coagulation times After 24 hours 100 mg daily for six days was *given* without further *appreciable* effect Following a blood *transfusion* there was a gradual decrease in prothrombin *and* coagulation times to a normal level on the eighth to tenth day *following transfusion* Normal values were restored even though 300 mg in divided dosage over four days had *been given following transfusion* Synthetic vitamin K substitutes were given during this period to ascertain if the prothrombin *time could* be maintained at a low level

CASE 6—Woman, 54 *with acute cholecystitis* developed thrombophlebitis in the right *leg* about eight days after admission Two days before dicoumarin *administration*, she was given sulfadiazine for a *total* dosage of 455 gr Dicoumarin compound, 300 mg *daily* was given *for four* days. There *was a* gradual increase of prothrombin *time* to 72 second with an increase *in* coagulation time to 24 minutes. An additional 300 mg was given *the eighth day* after the initial dose, with relatively little change in clotting power This was repeated on the eleventh day, *and four* days later prothrom

(8) Can M A J 46 14 18 March, 1942

bin time was 240 seconds and coagulation time 48 minutes Mild epistaxis occurred Through error an additional 400 mg dicoumarin compound was given and on the following day the patient became nervous and restless Two days after the la t 400 mg gingival bleedin⸗ was noted and there was *headache and general malaise Prothrombin time increased* to 420 second and coagulation time to 39 minute A 500 cc blood transfusion was given but its immediate effect on clotting power was not noted The following day there were pleural pain rales in the lung and some hemoptysis. There were flushing blood tinged vomitus gingival bleeding and mental depression Prothrombin time reached a maximum of 566 seconds six days after the last dose of dicoumarin Gross hematuria occurred during the height of elevation of prothrombin time Evidence of hemorrhage was widespread and another 500 cc transfusion and 2 methyl 1 4 naphtho quinone 1 mg every four hour five times daily orally were given There was a progres ively rapid fall in both pro thrombin and coagulation times to normal levels and bleed ing manifestations graduall, di appeared

All six patients showed prolongation of both prothrombin and coagulation times in 24 to 72 hours Sim ple experiments showed the effects of the hemorrhagic agent to wear off 8 10 days after withdrawal of the drug Three patients showed only moderate prolongation of prothrombin and coagulation times in two cases prolongation of prothrombin time was considerable and in one marked giving rise to multiple hemorrhages Method of administration and dosage did not vary greatly al though the response was variable Total dosage bore little relationship to the clotting disturbances induced At present there is no adequate control for hemorrhagic tendencies so induced Experiences of others show that transfusion is only of temporary benefit

DISEASES OF THE KIDNEY

The articles in this section are concerned with the etiology, clinical aspects and treatment of diseases of the kidney The concluding articles discuss the relationship between the kidney and hypertension —Eds

Classification of Albuminuria in adult males is discussed by Alexander Lyall[9] (Univ of Aberdeen) Of 20 000 men examined for recruitment 110 (0 55 per cent) showed albuminuria on more than one occasion They were divided as follows orthostatic albuminuria 28 per cent albuminuria without evidence of nephritis 20 per cent subacute nephritis 13 per cent subchronic or chronic nephritis 28 per cent and various urinary tract infections 11 per cent

The term orthostatic albuminuria was chosen for the first group in preference to adolescent albuminuria as the age group (18 35) was beyond the adolescent period and also in preference to benign albuminuria a term which includes some cases in the second group For inclusion in this classification the following criteria are essential (1) transient albuminuria and albumin free urine during rest (2) no pus cells red blood cells or renal casts in the urinary deposit (3) urea concentration over 3 per cent and normal blood urea value (4) no history of illness particularly a recent illness which might result in nephritis and (5) normal blood pressure and no clinical evidences of nephritis or anatomic abnormalities of the urinary tract

The albumin in the urine during activity varies from traces to considerable amounts (up to 0 2 per cent Esbach) In 18 of 31 cases large amounts occurred on initial examination In specimens collected the next day only traces were found except in one case There is suggestive evidence that the amount of albumin passed is increased with the temporary rise in blood pressure which often occurs during medical examinations as one manifestation of adrenal stimulation An occasional

(9) B M J 1 13 11 July 6 1941

hyaline or granular cast seen in the initial specimen may be neglected this occurred in six cases in this group Calcium oxalate crystals occur frequently but unless accompanied by red blood cells are not of pathologic significance

The albuminuria in the second group could not be classed as benign or orthostatic Each of the 22 cases presented some doubtful feature although evidence was insufficient to indicate definite interference with renal function Urea concentration was below normal in six cases with maximum concentration of 2 2 to 2 9 per cent urea In the others the concentration was normal Albuminuria was persistent in eight cases even at rest Occasional polyuria was found in two cases along with reduced urea concentration but without other abnormality Sediments presented an occasional granular or hyaline cast in five cases a few red blood cells in two and pus cells in six *Blood pressure* was elevated in five cases ranging up to 160/80 in this case the blood pressure during rest was 142/80 and in another the pressure was 154/90 during activity and fell to 120/74 during rest Only three patients had had scarlet fever one in conjunction with diphtheria and another with rheumatic fever In this group the individual case is difficult to evaluate

In the subacute nephritis group were 14 individuals aged 18 37 who showed either clinical or pathologic evidences of recent nephritis Various factors suggested that the lesion was recent and could be classified as acute or subacute nephritis With two exceptions all patients presented a history of illness, including sore throats severe chills influenza and cellulitis within the previous two months Scarlet fever had not been present in any cases In two cases edema of the hands and puffiness of the face were found Blood urea levels were increased to between 40 and 50 mg per cent in four cases Albuminuria was high (up to 0 3 per cent Esbach) and was constantly present Urea concentration tests gave maximum values of over 3 per cent in six cases and of less

than 2 5 per cent in one case only Sediments contained epithelial casts as evidence of acute renal desquamation in all but two cases Granular casts were frequently found and red blood cells were seen in all but two cases *Blood pressure* was 140 150 *systolic in five cases*, diastolic blood pressure was never above 88 mm Hg These cases indicate that milder degrees of subacute nephritis may occur in *men* who otherwise appear healthy *The* end result of such attacks is not known but in two cases the disease progressed to a subchronic stage

The chronic or subchronic *nephritis* group consisted of 31 individuals of whom 26 were 20 35 years of *age*, 18 and 47 being the age limits All presented continuous albuminuria *often* of considerable degree Blood urea was 20 52 mg per cent with values *over* 40 mg in seven cases The urea concentration factor lay below 70 in 11 cases in 7 of these it was below 50 The urea concentration test showed maximum values under 3 per cent *in* 17 in 13 they were below 2 1 per cent Sediments in all cases repeatedly revealed fairly numerous casts *usually* hyaline and granular in type Red blood cells were present in all except three cases Systolic blood *pressure* was 140 mm Hg or above in 15 cases and in 7 *of these* was over 150 the highest being 192 Diastolic pressures were 90 100 mm Hg in *seven* cases In 10 patients symptoms referable *to the* presence of chronic *renal* diseases were elicited on question only *Two* men complained of *headache* two of occasional frequency two of both these symptoms and *two* of backache and pain in the renal region Positive signs referable to *renal* disease were few In one case slight edema of the face and arms was present and one patient had dyspnea *on* exertion two were much under weight and one had aortic incompetence Two were anemic and one showed polycythemia History was negative in eight cases Three patients gave a history *of* having had scarlet fever before the age of 10 and one had had scarlet fever two years earlier In three there was a history of nephritis 2 11 and 12 years earlier and one patient whose blood

urea was 52 mg per cent and whose blood pressure was 164/94 was known to have had albuminuria 11 years previously Five men had had recurrent tonsillitis and nasopharyngeal infections were actually present in three Other previous illnesses included septic hands erysipelas compound tibial fracture rheumatic fever and exophthalmic goiter There was little evidence of urinary infection and cystitis was present in only one case All except two of these men were employed

The group with various urinary infections consisted of 12 men with albuminuria and whose urine on micro scopic examination revealed in addition hematuria or pyuria Two men had had nephrectomy one for tuber culosis and one for tumor In two cases renal calculi had been passed One man had had hematuria two years earlier and the remainder had had urinary infections with much pus in the urinary deposit

The Serum Antistreptolysin Titer in Chronic Glom erulonephritis and Its Relationship to Exacerbations were investigated by David P Earle Jr Emily N Loeb David Seegal John D Lyttle and Elizabeth L Jost[1] (Columbia Univ) A rise in serum antistreptoly sin titer was found to be of definite value in detecting group A hemolytic streptococcus infections in the pres ence of negative throat cultures in patients with chronic glomerulonephritis and of confirmatory value when the cultures were positive This test was not infallible since there were acute infections associated with positive cul tures for group A hemolytic streptococci which were not associated with rises in titer The sex of the patient was without apparent effect on the antistreptolysin titer re sponse to infection In general children exhibited greater response than adults The character of the pre ceding hemolytic streptococcus infection i e whether it was deep or superficial did not appear to affect the magnitude of the response Patients with nephrotic edema exhibited smaller rises in titer than did those without edema

(1) J Cl I t g t 1 483 489 491 49 J ly 1942

Thirty three exacerbations in chronic glomerulonephritis were observed in 15 of 81 nephritic patients Each exacerbation was preceded by an infection Twenty four of these exacerbations were associated with rise in serum antistreptolysin titer and six were not the data on three were inconclusive When a rise occurred the greater its magnitude the greater the incidence of associated exacerbations The exacerbation preceded the onset of the rise in seven of the eight sufficiently studied instances There was a high incidence of transient impairment of renal function in exacerbation associated with and also without rises in antistreptolysin titer

Exudative Interstitial Nephritis (Pyelonephritis) is reviewed by E T Bell[2] (Univ of Minnesota) Most infected kidneys show both pelvic and parenchymal involvement and may be appropriately designated pyelonephritic Cortical abscesses whether single or multiple often extend into the pelvis and may then be called pyelonephritis Pyelonephritis occurs both with and without urinary tract obstruction The obstructive type is about 12 times as frequent as the nonobstructive but attracts less attention since the renal symptoms are overshadowed by the major illness causing obstruction Obstructive lesions of the urethra bladder and prostate produce renal infection about twice as frequently as obstruction of the ureters above the bladder Renal infection subsequent to low urinary tract obstruction is considered to be ascending in nature whereas that resulting from ureteral obstruction is thought to be of hematogenous or lymphogenous origin Most pyelonephritides are due to colon bacilli (60 80 per cent) the remainder are due chiefly to staphylococci Frequently a colon bacillus infection is superimposed on a staphylococcic inflammation

In pyelonephritis associated with obstruction the clinical picture is usually dominated by the disease responsible for the hydronephrosis such as prostatic hypertrophy and carcinoma of the bladder or uterus but evi

(2) Su g ry 11 61 80 F b y 194

dence of infection, such as fever leukocytosis and pain or tenderness in the kidney region may be superimposed on those of the major illness The age and sex distribution of obstructive pyelonephritis corresponds to that of hydronephrosis Up to the age of 60 it predominates in females because of pregnancy and carcinoma of the uterus but thereafter there is a great preponderance in males chiefly because of prostatic disease

The pyelonephritis of pregnancy exhibits special features Hydronephrosis of some degree is nearly always present during pregnancy and this predisposes the kidneys to hematogenous infection About 1 per cent of pregnant women develop pyelitis Symptoms are chills fever leukocytosis, renal pain and pyuria Most patients may be cured by drainage and chemotherapy before onset of labor but 15 20 per cent of cases result in abortion or premature delivery Maternal mortality is about 3 per cent

Pyelonephritis during the puerperium is somewhat less common than during pregnancy and generally develops during the first week Pyelonephritis occasionally recurs during a subsequent pregnancy but there is no satisfactory evidence that it causes toxemia Rarely pyelonephritis of pregnancy continues as chronic pyelonephritis

In the paralytic and congenital types of hydronephrosis the associated pyelonephritis is easily recognized clinically In all forms of hydronephrosis infection destroys more or less of the renal parenchyma and hastens onset of uremia

The chief symptoms of acute hematogenous pyelonephritis are fever renal pain and tenderness pyuria leukocytosis and anemia The disease is relatively common during pregnancy in early childhood and in old age In children malformations of the urinary tract are a contributory cause and in older subjects diabetes is often a predisposing influence Prognosis is usually favorable In 50 cases reviewed by Bell there was usually an associated infectious disease which was largely re

sponsible for death and overshadowed to some extent symptoms which were directly referable to the kidneys

Hematogenous pyelonephritis persisting more than four months is considered chronic Symptoms vary with the severity of the disease Frequently there are acute exacerbations at irregular intervals during which the symptoms are more pronounced During exacerbations there are commonly fever leukocytosis renal tenderness or pain nausea pyuria etc In the intervals between acute attacks and in chronic forms of low intensity there may be only low grade fever loss of appetite or fatigability Pyuria is found only during exacerbations The disease may persist for years before terminating through uremia or infection Available evidence indicates that this disease seldom causes chronic hypertension

It is also probable that unilateral chronic atrophic pyelonephritis does not cause chronic hypertension but reports have been published of five cases in which blood pressure has remained normal for over a year after nephrectomy

Relation between Concentration of Total Protein and of Globulin in the Urine and Pathogenesis of Certain Renal Lesions in Bright s Disease Sam S Blackman Jr Willard E Goodwin and Mary V Buell[3] report an investigation of the role of hematuria albuminuria and globulinuria in causing accumulation in glomeruli and tubules of certain hyaline material which is partly responsible for the progressive renal failure in many cases of Bright s disease Repeated analyses of urinary proteins in cases of acute hemorrhagic nephritis lipoid nephrosis and chronic nephrotic nephritis reveal that high proportions of globulin are excreted in the urine at times These findings contrast with those of other investigators who making but few analyses in the individual case concluded that most of the urinary protein is composed of albumin

Results indicate that the element of renal insufficiency which is due to collection of fibrin hyaline and organized

(3) Bull. Johns Hopkins Hosp 69 397-467 November 1941

exudate within the kidney develops during periods when concentrations of total protein and of globulin are both high in the urine and that not only the fibrin but also the more abundant hyaline materials may represent precipitated globulins Two factors seemingly have special significance in causing the protein exudates to collect within the kidney namely concentration and duration of total proteinuria and globulinuria

In most of the cases of acute hemorrhagic nephritis there was proteinuria of low concentration and recovery occurred In cases of this character which were fatal there was little or no fibrinous or hyaline exudate in the kidneys In fatal cases of acute nephritis in which proteinuria and globulinuria occurred in high concentration it was shown that considerable quantities of fibrin may collect in the kidneys within a few days In these and in other cases whenever fibrin was found in the glomeruli it was always within Bowman s epithelial lined spaces

In the cases of chronic nephrotic nephritis some fibrin was found in the usual position but much more abundant was a different hyaline coagulum in glomeruli and tubules This material was found to collect in glomeruli almost exclusively in the walls and between the loops of individual capillaries In these cases renal failure progressed at a rapid or slow rate and the hyaline exudate in the kidneys in cases in which autopsy was done was more or less abundant depending on whether or not the urine frequently or seldom contained total protein and globulin in high concentration

Recovery occurred in nearly all cases of lipoid nephrosis Total protein concentration in the urine was frequently high but the proportion of globulin was usually low Maintenance of normal glomerular function in lipoid nephrosis absence of appreciable numbers of hyalinized glomeruli and scarcity of tubules obstructed by protein coagulums are probably all related to the fact that globulin is usually excreted in the urine in low concentration

The factors leading to precipitation of protein exudate

in glomeruli differ from those which may tend to cause precipitation within tubules Such variation may depend on the increased concentration of protein and salts in the tubules due to reabsorption of water by the epithelium so long as the cells are functioning

No correlation was apparent between the degree of hematuria and the concentration either of total protein or of globulin in the urine This is probably due to the fact that hematuria is the result of bleeding from relatively few widely separated glomerular capillaries while proteinuria is probably a more constant and diffuse phenomenon There was no histologic evidence that red blood cells or their pigmentary products took part in the formation of the permanent protein coagulums or scars within the kidneys in any case

Studies of cases in the terminal stages of renal failure revealed that proteinuria and globulinuria of high concentration are not caused either by renal failure per se or by the visible anatomic lesions responsible for chronic renal failure

In many cases of Bright s disease increased ingestion of fluids may prevent or retard the accumulation of protein coagulums in glomeruli and tubules by decreasing protein concentration in the glomerular filtrate

Serum Cholesterol and Atherosclerosis in Chronic Glomerulonephritis Alfred Steiner and Beatrice Domanski[4] (Columbia Univ) found atherosclerosis in 96 per cent of 54 patients aged 1 39 who died of renal disease in contrast to 35 per cent in a control group in the same age distribution The difference between the groups was more striking in the first two decades since atherosclerosis was present in 14 of 15 dying of renal disease in contrast to only 1 of 15 in the control group In addition the degree of lipoid infiltration when present in the control group, was less marked than in patients dying of renal disease This difference between the groups is more remarkable when compared with the incidence of atherosclerosis noted by Ophuls in a statis

(4) Am J M Sc 04 79 84 July 1942

tical survey of 3 000 autopsies Ophuls found only a few scattered cases during the first two decades 3 5 per cent during the third decade and 9 2 per cent during the fourth decade The greater incidence of atherosclerosis in the authors control group as compared to Ophuls large series may be explained in part by the interpretation of presence of atherosclerosis Presence of several raised yellow intimal lesions in either aorta or coronary arteries was regarded as sufficient for diagnosis of mild atherosclerosis

The data also indicated that hypercholesteremia almost invariably occurs in patients with chronic glomerulonephritis during some stage of the disease particularly in association with the nephrotic stage Likewise there is considerable fluctuation in the serum cholesterol levels in these patients in contrast to normal individuals in whom the cholesterol level has been found to remain relatively constant over long periods The hypercholesteremia which occurs in other diseases namely myxedema and poorly controlled diabetes is likewise associated with a high incidence of atherosclerosis It seems possible therefore that the elevation of serum cholesterol which occurs in renal disease is one of the factors responsible for the development of aortic and coronary atherosclerosis

It has also been demonstrated that atherosclerosis has occurred with great frequency in a young age group in which atherosclerosis ordinarily is relatively rare For this reason the etiologic significance of senescence which is frequently considered paramount in the development of atherosclerosis can be minimized at least as far as the present study is concerned

Histopathologic Studies of Diabetic Kidneys with Special Reference to Changes in Glomeruli, were conducted by R Murakami[5] in 27 cases of diabetes mellitus *in 7 of which death resulted from acidosis* The most striking changes noted were enlargement of the glomeruli due to both regressive cellular swelling of the

[5] T ky Igakkw I Z ai 55 528 53 July 1941

in glomeruli differ from those which may tend to cause precipitation within tubules Such variation may depend on the increased concentration of protein and salts in the tubules due to reabsorption of water by the epithelium so long as the cells are functioning

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(4) Am J M Sc 04 984 J ly 1942

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(5) Toky Ig kkw i Z 1 55 5 9 32 J ly 1941

basement membrane and progressive hypertrophy and hyperplasia accompanied by hyperemia Hyalinization fibrotic union of capsules and fatty and glycogen degeneration of the parenchyma were also noted All these changes in some instances at least appeared to be reversible paralleling the clinical course in each case, but parenchymatous degeneration was not clearly demonstrable in cases of acidotic coma or of renal complications The pathologic changes of the diabetic kidney resemble those seen in nephrosclerosis but the two conditions can be cytologically differentiated The changes may be regarded as a cumulative product compensatory to functional disturbances caused by the stimulating effect of overfunctioning organs and tissues saturated with the abnormal composition of urine The predominance of these changes occurring in the glomeruli and the terminal capillaries may be due to the chief excretory function which these tissues perform and to the contributory effect of the specialized structure of the glomerular tufts Epithelial cells at the end of Bowman's capsule are probably only an extension of the main epithelium Although there is no direct evidence of any organic relation between this and other lipemic diseases the abnormal enlargement of the glomerular tufts may aggravate the lipemic kidney and accentuate such diseases by epithelial hypertrophy The diabetic kidney may thus be regarded as representing a case of glyconephrosis under the general category of glomerular nephrosis

[The next two articles deal with tests of renal function The article by Talbott includes a clear statement of the essence of the newer clearance tests developed especially by Homer Smith and his associates —Eds]

Renal Function Tests are discussed by John H Talbott[6] (Harvard Univ) Commonly used tests of renal function include those testing ability to concentrate solids and to excrete phenolsulfonphthalein intravenous pyelography and the determination of serum nonprotein nitrogen All yield useful information but they are

(6) New Engl nd J Med. 26 197 01

neither quantitatively precise nor sufficiently accurate to detect small variations from the normal or to detect the early changes of anatomic renal disease For example each test may yield normal results when more precise tests will show a deficiency as great as 30 per cent in the amount of blood passing through the kidney or in the amount of glomerular filtrate formed To obtain information regarding these functions clearance tests must be used

Urea clearance and creatinine clearance have been superseded by inulin and diodrast clearance tests Urea appears in glomerular filtrate but a variable amount depending on diuresis is reabsorbed by tubular activity Likewise creatinine appears in glomerular filtrate and an additional amount is excreted by the tubular cells Since the clearance of both substances is an index of combined glomerular and tubular activity they are less attractive than subsequently devised clearance tests which measure specific functions separately Clearance tests are performed while the patient is fasting and lying supine Continuous intravenous injection is maintained throughout the test A soft rubber catheter is retained in the bladder and urine is delivered without interruption into a container The four tests may be performed in about three hours Talbott discusses the tests for renal function

Inulin Clearance —Inulin clearance (C_I) is used synonymously with rate of formation of glomerular filtrate Approximately 25 Gm inulin is necessary for a single test Inulin is not metabolized and is excreted by the kidneys if injected intravenously Excretion occurs exclusively through the glomerular membrane the tubules neither reabsorb nor excrete the substance As an example if the plasma level of inulin is 100 mg per cent and if 125 mg inulin is excreted by the kidneys into the bladder per minute 125 cc plasma must have participated in the formation of glomerular filtrate to allow this quantity of inulin to be excreted The amount of inulin cleared by the kidneys and the amount of

glomerular filtrate formed per minute are identical These values are expressed as cubic centimeters of plasma cleared per minute An average value is 125 cc per minute and the normal range is 100 150 cc per minute Values should be corrected to a standard body surface area and Smith selected 1 73 sq M as the standard in his studies

Diodrast Clearance —Diodrast clearance (C_D) is assumed to measure effective renal blood flow i e effective so far as urine formation is concerned The diodrast used in the determination is the same as that employed in intravenous pyelography At low blood concentrations approximately 1 mg per cent of plasma, all diodrast entering the arterioles contiguous to functioning nephrons is removed before the blood leaves the kidney A portion is removed by the glomeruli and the remainder is excreted by the tubules It makes little difference for the calculation of renal blood flow how the nephron removes the diodrast the significant point is that removal is complete in the venous blood returning from the kidneys Diodrast like inulin is not destroyed by the body and approximately all diodrast in the blood is eventually excreted If the plasma concentration of diodrast is 1 mg per cent and if 7 mg diodrast is excreted per minute into the bladder 700 cc plasma must have passed through the kidneys to permit such excretion Renal plasma flow or C_D therefore is 700 cc per minute If whole blood contains 40 per cent cells and 60 per cent plasma the effective renal flow of whole blood would be approximately 1 200 cc per minute The average normal renal flow of whole blood is 1 200 cc per minute and the range is 1 000 1 400 cc

Tubular Excretion of Diodrast —Tm_D is the designation for maximal capacity of the tubules to excrete diodrast when a greater quantity is presented to them than they are able to handle This may be determined if plasma diodrast is elevated to 25 mg per cent At such levels, not all the diodrast is extracted from the blood as it is at low plasma levels and a portion of the diodrast

appears in each of three fluids The first portion appears in the glomerular filtrate at the same concentration as it exists in the plasma The second portion is excreted into the tubules by the tubular cells The urinary excretion of diodrast is composed of these two portions If the total urinary excretion and the amount presumably excreted by glomerular filtration are known the difference is the amount excreted by the tubular epithelium This constitutes the value Tm_D The third portion is that left in the blood after the tubular cells have functioned maximally This portion is disregarded For example if plasma diodrast concentration is 25 mg per cent and the rate of *glomerular filtrate formation is 125 cc per minute 30* mg diodrast per minute is excreted through the glomeruli If a total of 80 mg per minute is excreted into the bladder the difference between the total urinary excretion (80 mg) and the amount present in glomerular filtrate (30 mg) gives a value of 50 mg for Tm_D a normal figure for tubular excretion of diodrast

Tubular Reabsorption of Glucose —Tm_G is an index of the maximal capacity of the tubules to reabsorb a specific substance glucose when an excessive amount is presented to them Thus while Tm_D measures maximum capacity of the tubules to excrete a specific substance (diodrast) Tm_G measures their capacity to reabsorb a specific substance (glucose) For example if plasma glucose concentration is elevated to 400 mg per cent and the rate formation of glomerular filtrate is 125 cc per minute 500 mg glucose will appear in glomerular filtrate per minute If only 200 mg per minute appears in the urinary bladder the difference between glomerular excretion (500 mg) and total excretion (200 mg) gives a value of 300 mg for Tm_G the maximum amount *reabsorbed from the filtrate by the tubular cells* This is an average figure

Renal Concentration Test Employing Posterior Pituitary Extract William A Sodeman and Hugo T Engelhardt[7] (Tulane Univ) describe a procedure using

(7) Am J M S 03 812 818 J 194

posterior pituitary extract for determination of renal tubular function It differs from the usual concentration tests in that long periods of fluid restriction are not necessary Unprepared patients, after voiding are given 0 5 cc posterior pituitary extract (10 units) subcutaneously and four specimens are collected at half hourly intervals thereafter Specific gravities determined in the pyknometer or with the Saxe urinopyknometer which uses only 4 cc urine may be used as an index of renal tubular function

The authors have not used the procedure in patients with marked oliguria pregnancy angina pectoris or myocardial infarction In the presence of congestive heart failure with diuresis active from treatment the use of concentration tests is unsatisfactory because of the water diuresis from edema fluid and the inability to obtain adequate specific gravity determinations

[The next four articles are concerned with treatment of nephritis —Eds]

Diet and Bright s Disease The late Soma Weiss[8] (Harvard Univ) discussed rationale of diets in various syndromes associated with Bright's disease, as evolved from consideration of the structural, physiologic and chemical deviations from the norm occurring therein

Early Stages of Acute Glomerulonephritis and Interstitial Nephritis with Oliguria —In acute diffuse glomerulonephritis and acute interstitial nephritis, as well as in cortical necrosis of the kidney oliguria, arising from both intrarenal and extrarenal factors is common Thus in addition to acute obstructive glomerular factors interfering with filtrate formation and to tubular obstruction interfering with filtrate flow extracellular factors such as low blood sodium and hypoproteinemia are also responsible During edema formation fluid and sodium chloride escape into the tissues and fail to reach the kidneys Low osmotic blood pressure caused by hypoproteinemia is significant in causing sodium retention in the tissue Dietary management in this stage

[8] [illegible] M J 5 4?6 01 July 1941

depends on the relative roles of these intrarenal and extrarenal factors The amount of fluid and salt given depends on the water sodium chloride protein and nitrogen content of the plasma on urine volume and on weight change all of which factors should be measured daily

The patient may be placed for three to five days on a Karell milk diet increasing calories by adding fruit juice and lactose Subsequently however total daily fluid intake should seldom be less than 1 500 cc This amount corresponding to the average water loss through the skin and lungs should be maintained even in the presence of edema and normal chloride content of the plasma except for 7 to 10 days If severe edema or nervous symptoms necessitate more prolonged fluid restriction total daily intake should be estimated by giving 1 500 cc plus the volume of the oliguric urine If the oliguric urine has a low specific gravity and there is nitrogen retention fluid intake should not be restricted below 2 000 cc because of danger of uremia Since water is retained in the body as salt solution even a fairly large amount of water will aggravate the edema less if sodium salts are not available With plasma chloride concentration above 9 , m Eq therefore diet in this acute stage should contain minimal sodium chloride up to 2 5 Gm With a lower concentration a temporary increase in salt administration is indicated In the presence of hard edema (nephritic edema) associated with normal or with only slightly reduced plasma protein an excess of sodium salts in particular is prone to precipitate cerebral symptoms In the presence of soft edema (nephrotic edema) sodium salts are less likely to cause symptoms or other harmful effects

Although there is no clinical evidence indicating that protein harms either the normal or the diseased kidney restriction of protein diet is advisable for two to three weeks during the initial oliguric stage of nephritis At this stage a 1 500 2 000 calorie carbohydrate diet

reenforced with vitamin concentrates is given Such a diet will decrease the intrinsic protein metabolism of the body

With subsequent improvement of renal function and nitrogen retention and with subsidence of oliguria fluid intake is raised gradually and the diet should now contain 30 60 Gm protein The rest of the food should be chiefly carbohydrates with some fat Salt restriction (less than 2 Gm sodium chloride) should be continued Addition of organic sodium salt to the diet is contraindicated Use of lemon lime and certain vegetable and root extracts will increase food palatability An acid ash diet with low sodium will be helpful If the low sodium chloride diet is not palliative 2 5 Gm potassium chloride or potassium nitrate may be added to the food although it is controversial whether potassium salts are specifically helpful in treatment of edema As glomerulonephritis reaches the more chronic stage dietary protein should be 10 15 per cent of the total calories i e 80 120 Gm A higher protein diet is not indicated

In patients with focal (hemorrhagic) glomerulonephritis often associated with gross hematuria which sometimes accompanies pneumonia and other infectious diseases, symptoms and edema are usually absent and special diet is not indicated Patients with oliguria due to renal damage caused by transfusion reaction immediately require an alkaline urine to prevent precipitation of hemoglobin in the renal tubules

Nephrotic Syndrome —This usually develops during the subacute or early chronic stage of glomerulonephritis The soft, diffuse and massive edema of the syndrome, partially dependent on gravity is caused primarily by lowered osmotic blood pressure the hypoproteinemia in turn originating from the severe or long continued proteinuria It is problematic whether protein synthesis is normal or impaired The latter concept is consonant with clinical evidence that a high protein diet is frequently unsuccessful in raising plasma protein content Nevertheless, high protein and sodium r_ * with

2 000 cc of fluids should be tested for weeks on every patient with subacute or chronic nephrotic syndrome At no time however must limitation of salt and fluids interfere with food consumption particularly proteins

Pyelonephritis —In acute pyelonephritis caused by Bacillus coli infections ketogenic diets are no longer used for a combination of acid producing salts and mandelic acid is more effective and better tolerated When sulfanilamide is used fluid intake should be regulated so that urinary volume does not exceed 500 700 cc per diem [Fluid restriction is now regarded as unnecessary —Eds] *Sulfanilamide is usually ineffective* when renal function is impaired If pyelonephritis is accompanied by renal failure or uremia the dietary regimes are the same as in other types of chronic Bright s disease

Chronic Bright s Disease without Edema —Patients with chronic Bright s disease present many common features regardless of the nature of the initial renal lesion (i e glomerulonephritis nephrosclerosis pyelonephritis glomerulonephrosis of toxemia of pregnancy interstitial nephritis glomerulosclerosis or congenital hypoplasia) The chronic stage of each of these diseases presents a scarred kidney greatly reduced in size The number of nephrons present is greatly reduced and many of the remaining ones are injured the arterial vessels are also diseased Consequently kidney reserve is impaired as the hyposthenuria indicates hypertension is present and edema is usually absent or if present is usually nephrotic or cardiac in origin

Dietary measures are directed at building up or maintaining optimal nutrition Dietary protein should be 80 120 Gm for prolonged protein restriction results in bodily and cardiac weakness anemia and other untoward reactions If edema is not present salt restriction should not be practiced but if it is present its nature should be investigated and it should be treated accordingly In the absence of edema water intake should not be restricted but should not be excessive

Alcohol tea and coffee in moderation are permissible

Arterial Hypertension —Hypertension associated with edema such as that occurring in acute glomerulonephritis interstitial nephritis and glomerulonephrosis of toxemia of pregnancy is amenable to dietary measures in contradistinction to the hypertension of chronic Bright s disease without edema wherein diet plays little or no role

In acute Bright s disease hypertension is usually associated with cerebral symptoms and with hard (nephritic) edema Sodium restriction improves the symptoms and the edema and reduces this type of hypertension conversely free administration of sodium chloride or of soda accentuates the hypertension and aggravates the symptoms Serious or fatal convulsions can result from indiscriminate use of sodium salts in this type of hypertension Even if some urinary retention is present the seizures do not represent true uremia, but special types of encephalopathy A low sodium diet should be given containing 1 500 calories 1,500 2 000 cc fluids 40 60 Gm protein 160 Gm carbohydrate and 80 Gm fat

Low sodium diet on the other hand exerts no beneficial effect on the hypertension of chronic Bright s disease regardless of its origin and the prolonged use of such a diet may weaken the patient Even excessive use of salt by such patients does not increase hypertension or accentuate symptoms

Renal Failure and Uremia of Chronic Bright s Disease — As the kidney loses its capacity to concentrate the filtrate in progressive renal failure more water must be excreted to facilitate electrolyte discharge Subsequently, inorganic acids phosphates and sulfates in particular accumulate in the body Chlorides on the other hand, continue to be swept out with the diluted urine Sodium of the blood plasma and interstitial fluids is used increasingly as a base in the elimination of acids Sodium depletion is frequently accelerated also by vomiting or diarrhea All these fa[illegible] enhance

the tendency to acidosis and dehydration With the lowering of tissue fluids and sodium the plasma volume decreases and the impaired renal flow hastens complete disintegration Simultaneously the blood calcium becomes low due to hypoproteinemia and phosphate retention Anemia seemingly the result of depressed bone marrow function develops

Treatment is in many respects the opposite of that practiced in acute nephritis with edema As edema is usually absent when nitrogenous products accumulate water can be administered freely but more than 2 500 3 000 cc is seldom indicated Depending on the stage or rate of renal failure moderate (40 80 Gm) or severe protein restriction should be instituted As a rule the diet should contain 7 10 Gm sodium chloride to compensate for the loss in the urine Whenever a base is needed addition of the malate citrate or tartrate of sodium is useful but when salt is to be restricted there is no virtue in giving these organic sodium salts Sodium chloride administration can be gaged by the plasma sodium chloride content which should be kept at 96 102 m Eq If acidosis is present the addition of 2 to 3 Gm sodium bicarbonate may be tested Vegetables and fruit juices yield relatively high amounts of base as well as of potassium However loss of renal regulatory function on the acid base balance results in easy precipitation of alkalosis

The anemia of nephritis responds to diet only if it is caused by dietary deficiency or by blood loss The anemia of chronic Bright s disease is refractive to dietary or other therapeutic measures

Treatment of Acute Nephritis Observations by Francis D Murphy and Bruno J Peters[9] (Marquette Univ) do not support the contention that nearly all patients with acute nephritis recover but indicate that in many the acute episode is followed by a variable period of 2 to 24 months in which careful urinalysis reveals evidence of an inflammatory renal lesion This

(9) J A M A 118 183 188 J 17 194

regularly falls in subjects with acute nephritis or eclampsia but is frequently unaffected in those with chronic cardiovascular disease In this last group beneficial effects were irregular in contrast to the much more consistent fall in blood pressure with clinical improvement in the subjects with acute nephritis and eclampsia

Use of Sulfanilamide in Treatment of Acute Glomerular Nephritis Robert H Williams, Warfield T Longcope and Charles A Janeway (Johns Hopkins Univ) report a comparative study of the course of acute hemorrhagic nephritis in 42 individuals treated in essentially the same manner as 108 individuals except that in the former group sulfanilamide was administered Most patients were followed two to six years or longer The great value of effecting complete cure in acute nephritis lies in the fact that once the nephritis has healed recurrence is rare even though the patient experiences one or more serious infections due to hemolytic streptococcus Sulfanilamide was used almost exclusively for patients from whom beta hemolytic streptococci were cultured from some focus and who had a well defined acute onset of their nephritis within two months, in most instances within a few days

Dosage varied from 1 2 to 6 Gm daily the usual being 2 4 or 3 6 Gm divided into six equal doses Average total dosage was 49 Gm with range from 6 to 169 Gm Blood concentrations of the drug ranging from 4 5 to 18 mg per cent varied more from day to day than in patients with nonrenal conditions a circumstance attributed to the frequently changing renal function Mild toxic reactions developed in three patients

In the sulfanilamide treated group there was one death in the acute stage Complete recovery occurred in 15 of 33 patients who returned for observation after six months and in 29 of the 39 patients followed for at least two years Three additional patients followed for only a few weeks are in the quiescent stage Five of the 39

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patients who were followed two years or more are in the quiescent stage and 2 are in a progressive stage

In the control group of 108 patients there were 12 *deaths in the acute stage and 5 deaths following a progression* to chronic nephritis There are only 56 complete recoveries (52 per cent) 11 are in a quiescent and 24 in the chronic progressive stage

Thus in most respects the 42 patients receiving sulfanilamide have shown more rapid improvement than the 108 controls This has occurred despite the fact that there was relatively little difference in the type or severity *of the initial infection the interval from infection* to onset of the nephritis type or severity of the nephritis or interval between onset of nephritis and admission The use of sulfanilamide has resulted in most *instances in great reduction in the number of beta hemolytic* streptococci in the throat or other foci of infection This antibacterial effect apparently did not interfere with the immunologic response as exhibited by the anti*streptolysin titer of the blood serum because the quantitative* changes in the serum bore the same relationship to the course of the disease in the treated group as in the controls Albumin and formed elements disappeared *from the urine faster in the former group Kidney function* as indicated by urea clearance and phenosulfonephthalein tests exhibited a definitely greater improvement and the edema and hypertension were of shorter *duration Of greatest importance was the fact that the* incidence of recoveries was greater and the number of patients pursuing a progressive course distinctly less in the sulfanilamide treated group

Frequent urinalyses and *kidney function tests failed* to demonstrate that sulfanilamide had caused any renal damage either in these or in other patients This is true despite the fact that most patients had edema hypertension large quantities of albumin with formed elements in the urine and elevation of the nonprotein nitrogen of the blood at the time chemotherapy was started

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(2) Am J M Sc 03 157 3

normal volume of urine flow is reestablished The pelves should be irrigated at two hour intervals with warm (107 F) distilled water This procedure is effective in relieving extrarenal obstruction an intense diuretic regimen is necessary to relieve intratubular renal obstruction

The diuretics should be large quantities of fluid and if necessary hypertonic dextrose solutions If possible, use *of magnesium sulfate should be avoided as it* has been suggested that it predisposes to sulfhemoglobin formation but it may be used intravenously if there is no cyanosis and if oliguria persists after other measures for diuresis have failed Mercuric and acid diuretics should not be used The patient should be placed on an alkaline ash diet and the urine kept alkaline with sodium bicarbonate Protein intake should be restricted for four or five days or during the period of severe oliguria hematuria and azotemia Fluids should be administered in large quantities for many days after the kidneys have returned to normal The patient should be followed for evidence of residual or latent damage

Specific Morphology of Crystals Appearing in Urine during Administration of Sulfanilamide Derivatives David Lehr and William Antopol[5] (Newark N J Beth Israel Hosp) describe characteristic crystal shapes occurring in human urine during administration of sulfapyridine sulfathiazole sulfadiazine and sulfaguanidine Figures 66-68 show crystals found during study of 19 patients receiving sulfapyridine All three types are made up almost entirely of acetylsulfapyridine and contain negligible traces of the free compound They are transparent and colorless Both whetstones and arrowheads may be present in the same specimen The centrally waisted sheaves are somewhat rarer owing to their large size the sediment has a coarse granular appearance They may be occasionally interspersed in urines containing arrowheads or whetstones in abundance

(5) Am J Cl P th 1 00 208 Ap l, 1942

[Renal complications are an important aspect of chemotherapy with sulfonamides, a subject considered in the next two articles —Eds]

Renal Complications Following Sulfathiazole Therapy Travis Winsor and George E Burch[4] (Tulane Univ) have observed six cases in which renal injury developed following administration of sulfathiazole Three were fatal Diagnosis of such renal damage is not difficult especially if the patient has been properly studied and inventory of the renal state has been taken before sulfathiazole administration The appearance of hematuria oliguria backache tenderness over one or both kidney areas decreased renal function azotemia and progressive nephromegaly in a patient who has received sulfathiazole suggests renal damage from the drug Rarely do all the findings exist at the same time Cystoscopic study usually establishes the diagnosis Sulfathiazole crystals in the urine may aid diagnosis but their presence alone does not mean renal damage X ray study will usually not reveal uroliths unless there is calcification which is rare It should be remembered that renal damage can occur in the presence of a low blood level of sulfathiazole and also after only a small amount of the drug has been given

To reduce incidence of such renal damage certain rules should be followed (1) Check previous sulfonamide medication to prevent overdosage (2) Evaluate the state of renal function before the drug is administered and proceed accordingly (3) Evaluate the state of hydration to insure a large volume of urine (4) It is preferable to maintain an alkaline urine during sulfathiazole administration (5) Guard against allergy hypersensitivity and idiosyncrasy

Administration of the drug should be stopped immediately on the slightest evidence of kidney damage Fluids should be administered in large quantities Ureteral catheterization should be done promptly and the catheter should be allowed to remain in place until a

eccentric bindings and shell forms (Fig 70) Free sulfadiazine is the only one of the four compounds which has a lower solubility than its acetylated derivative this *explains its precipitation as a free drug in the urine*

Sulfaguanidine crystals are simple rectangular oblong plates with slight bulgings in the long axis They are either glass clear or have a fine meshlike pattern which makes them appear like isolated plant cells or slender



Fig 68 —U[illegible]

tapeworm proglottides They tend to conglomerate forming cross or starlike structures Repeatedly slender sheaves of needle crystals are seen interspersed *among the plates They vary in size from 0 02 × 0 09 to 0 0[illegible] × 0 24 mm*

The frequency and quantity of the appearance of crystals in the urine are apparently closely related to the solubility of the sulfanilamide compounds and their acetylated derivatives The acetyl derivatives formed in the body from sulfapyridine sulfathiazole and sulfadiazine show a depressed melting point and a solubility

In studies of urines of 114 patients receiving sulfa thiazole three characteristic shapes were noted The crystals consist of acetylsulfathiazole and often appear simultaneously (Fig 69) The commonest type resembles dumb bells or shocks of wheat with a central binding The crystals start as slender sheaves and grow so that the two half circles close up to form rosettes 0 004 × 0 6 to 0 6 × 0 08 mm Another type rosettes are rodlike



Fig 66 (left) —L ns y t l f s (l alfapyridine Most common f m wh t n wh h r g e tly u s d e t p (l l s and u lly sh w n t h g t n f n o L th dge
Fig 6 (right) —A tyl ulf p d n Ar wh d m l r to wh t t k but u dg b yed w th n h rp j t d w) k d nt fe t f n r t th d b r und d w th gul n t h ng

structures about 0 04 × 0 1 mm and may represent a crystalline cast Hexagonal platelets 0 04 × 0 06 to 0 15 × 0 02 mm represent the third type They are usually amber green sometimes glass clear and have a distinct envelope like pattern Rarely in urine of low specific gravity slender petal shaped structures are observed interspersed among the typical forms

Sulfadiazine crystals differ from sulfathiazole crystals in the asymmetrical arrangement of the sulfadiazine primary structures with resultant shocks of wheat with

Unilateral Renal Atrophy Associated with Hypertension The incidence of hypertension was determined in 84 cases of unilateral renal atrophy and 13 cases of unilateral renal hypoplasia by Archie H Baggenstoss and Nelson W Barker[9] (Mayo Clinic) There were 48 cases of pyelonephritic atrophy 28 of hydronephrotic atrophy and 8 of pyonephrotic atrophy Death in most



Fg 70 —Cry t l u ry p m n 24 hou ft t tm t had be wit h d f m lf th l t ulf di P f t h ck f wh t with t b d g' (tyl ulf d) m ng ymm t l dumb-bell (tyl lf th l) lso typ l ph ph t nd m t ry tal

cases was due to neoplastic disease or infection Hypertension caused death in only five cases Only in the cases of pyelonephritic atrophy (39 6 per cent) and of pyonephrotic atrophy (37 5 per cent) was the incidence of hypertension greater than in the control group (29 per cent) Incidence of hypertension was 41 9 per cent in the cases of pyelonephritic atrophy in which the atrophied kidney weighed 75 Gm or less and 35 4 per cent in those in which the atrophied kidney weighed over 75 Gm

In 20 of the 48 cases of pyelonephritic atrophy and 12 of 25 cases of hydronephrotic atrophy there was

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which is about twice as high as that of the chemically pure drugs Thus the morphology of urinary crystals seems to be dependent on an "impurity" which is contained in these structures their peculiar shape points to the influence of colloids on the crystal formation In a *few instances the crystals found in the urine deviated* significantly from the typical appearance described, the



Fig 69 —Urinary crystals of acetylsulfathiazole simultaneous presence among urinary p m n f th e f rm dumbbell r tte and hexagonal plat let F t tw f ms pp a amber gr n nd show p on un ed rad l tr t p th d om t m ry th n gla lear but mo ften th k amb gr n w th n el p lk p tt n

urine in these cases was either strongly alkaline or of very low specific gravity Change in composition of the urine may account for the fact that specimens from the same patients often present a shift from one crystal form to another

The in vitro formation of urinary crystals occurs most easily with acetylsulfadiazine next with acetylsulfathiazole and is most difficult with acetylsulfapyridine

[The concluding articles in this section are devoted to the relationship of renal disease and hypertension Many of the articles deserve careful study in the original if *even the present knowledge* of the situation is to be comprehended —Eds]

Effective Renal Blood Flow in Subjects with Essential Hypertension William Goldring Herbert Chasis Hilmert A Ranges and Homer W Smith (New York Univ) examined the glomerular filtration rate (C_{IN}) diodrast clearance (C_D) and the maximal rate of tubular excretion of diodrast (Tm_D) in 60 subjects with essential hypertension and compared these data with those obtained for the normal kidney

An extreme reduction in Tm_D occurs in advanced stages of the disease and for the entire series Tm_D is below or in the lower range This suggests that the disease is characterized by progressive impairment of tubular function which proceeds at varying pace in different subjects

In some individuals impairment of tubular function appears to outrun impairment of glomerular function (formation of impotent tubules) so that the filtration rate remains within the limits of normal variation when Tm_D has been substantially reduced In the nature of the renal circulation elevation of the mean systemic blood pressure or the formation of impotent tubules may increase the quantity of diodrast containing blood perfusing the residual functional tissue The authors believe that in either case the anomalous condition will be revealed by the presence of a high filtration rate per unit of functional tissue Deleting such anomalous instances the effective blood flow per unit of functional tubular tissue or the ratio C_D/Tm_D in the remaining subjects ranges downward from the mean normal to highly subnormal values indicating relative renal ischemia Since this ischemia is associated with an elevation of the filtration fraction it is attributed to increased tone of the efferent glomerular arterioles On the available evidence this increased efferent tone may in turn be attributed to the presence of one or more pressor substances in the blood The increased efferent tone is functionally reversible in that renal hyperemia associated with a fall in filtration fraction (efferent

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some degree of active inflammation in the opposite kidney Inflammation in the opposite kidney was present more often in cases in which hypertension was a feature than in those in which it was *not observed*

The degree of arteriosclerosis in the opposite nonatrophic kidney was generally less severe than in the atrophied kidney In 8 of 19 cases of pyelonephritic atrophy associated with hypertension the blood vessels were considered normal for the age of the patient

These observations suggest that unilateral pyelonephritic atrophy is more often associated with hyper*tension than would be expected on a basis of chance* They also suggest that hypertension is more likely to be present if the degree of atrophy is severe As ab*normal* vascular changes *had not occurred* in the opposite nonatrophic kidney in a number of cases of unilateral renal atrophy associated with hypertension, it is suggested that in many cases in which hypertension is in an early or mild stage it may not be associated with renal arteriosclerosis

Effective Renal Blood Flow in the Separate Kidneys of Subjects with Essential Hypertension Herbert *Chasis and Jules Redish*[1] *(New York Univ) applied* the clearance method to the measurement of renal blood flow filtration rate and tubular excretory mass in the separate kidneys of patients with essential hypertension Results indicate that the destruction of tubular tissue progresses equally on the two sides in hypertensive disease and that the functional disturbance in respect to blood flow and filtration rate is shared equally by the two kidneys *In no instance* was there any indication of a unilateral ischemic kidney If it is predicated that renal ischemia is the primary causal factor in all essential hypertension, it would be expected that unilateral impairment of renal function would be observed *more frequently than bilateral impairment* The absence of unilateral impairment in these subjects argues against this premise

(1) *J Clin. Investigation* 20 655 661 November 1941

Renal Circulation in Normal Individuals and in Hypertensive and Renal Disease Kurt Steinitz[3] (Istanbul) found the mean normal values of renal plasma flow (diodrast clearance) and of glomerular filtration (inulin clearance) to be in the same range as those reported by Smith In four of six cases of essential hypertension the renal blood flow and the glomerular filtration were found to be within normal range This leads *to the conclusion that a decrease* of the renal blood flow is not a necessary and characteristic attribute of essential hypertension and suggests that essential hypertension be distinguished as a special disease from renal hypertension

Hypertension and Pressor Activity of Heated Extracts of Human Kidneys Eugene M Landis[5] (Univ of Virginia) reports that whereas intravenous injection in rabbits of simple saline extracts of normal and abnormal human kidneys was often lethal and usually strikingly depressor freshly prepared heated extracts of human kidneys did not depress blood pressure and were never lethal when injected immediately after heating and filtration After standing at room temperature for several hours or in the refrigerator for 24 hours a previously innocuous extract usually became depressor or even lethal once more These effects could be abolished again by reheating

Heated kidney extracts were either entirely inert producing *no perceptible effect on blood pressure or pulse* rate or were moderately pressor in some instances Active extracts produced maximal pressor effect in 2 to 5 minutes the elevation persisted for 30 to 45 minutes or until interrupted by injection of rabbit kidney extract at the end of 10 minutes

Of 16 extracts prepared from normal human kidneys and injected into anesthetized nephrectomized rabbits 10 were inert and 6 elevated blood pressure 5 15 mm Hg Of 36 extracts prepared from the kidneys of hypertensive persons 20 were inert while 16 raised

(3) A t m d S d 109 95 114 No mbe 1941
(5) Am J M S 20 14 19 J ly 1941

dilatation) follows the administration of suitable doses of pyrogen as in normal subjects The absolute values of C_D/Tm_D in hypertensive subjects during hyperemia are of the same order of magnitude as in normals during the hyperemic reaction

In most hypertensive subjects Tm_D was reasonably constant over a considerable period and was not increased during pyrogenic hyperemia In some subjects, however, Tm_D was increased during hyperemia, indicating that in these and perhaps in other subjects substantial quantities of tubular tissue may be ischemic under basal conditions Spontaneous changes in Tm_D have been observed which may reflect changes in the quantity of tubular tissue available to perfusion or trophic changes in the excretory tissue itself

In brief the functional picture presented by the hypertensive kidney is consonant with the theory that there is present in the blood in hypertensive disease one or more pressor substances which produce a reversible renal ischemia by constriction of the efferent glomerular arterioles In addition there are profound impairment and ultimate destruction of tubular function Which of these precedes the other is as yet undetermined

There is no evidence to warrant the conclusion that renal ischemia is the primary cause of essential hypertension The renal ischemia demonstrated here which has its origin in increased tone of the efferent glomerular arterioles appears to be one of the sequelae of the hypertensive process The authors believe that primary renal ischemia in man can under proper quantitative circumstances initiate a hypertensive process but whether or not the secondary ischemia associated with efferent hypertonus which is present in hypertensive subjects generally contributes to the progress of the disease has not been determined Alternatively, the possibility cannot be excluded that the appearance of pressor and cytotoxic substances in the blood follows a metabolic disorder in the kidney or in other organs and is wholly independent of renal ischemia

in any way invalidate the humoral hypothesis of hypertension but emphasizes the necessity of studying active substances in blood during life for clear differentiation

Cardiac Factor in the Pressor Effects of Renin and Angiotonin Experiments conducted by W H Philip Hill and E Cowles Andrus[6] (Johns Hopkins Univ) show that angiotonin constricts the coronary arteries and increases the amplitude of contraction of the isolated saline perfused heart of the cat and as does also renin augments the output and arterial pressure of the heart lung preparation Certain of these conditions bear significantly on the probable action of these substances in the intact animal It is presumed that renin is inactive in the saline medium because of the lack of activator the need of angiotonin activator is apparently less imperative Moreover it is inherent in the Langendorff method used herein that the pressure head at the ostia of the coronary arteries is maintained constant and uninfluenced by the heart beat coronary constriction is thus directly reflected in decreased coronary flow In vivo on the other hand the results of coronary constriction may be masked or even overbalanced by a concomitant arterial pressure rise In the heart lung preparation cardiac output and arterial pressure are increased by angiotonin or renin despite a constant or even diminishing inflow pressure and against a constant peripheral resistance Since cardiac rate is not increased this can only mean that the amplitude or vigor of ventricular systole is enhanced In the intact animal this may be expected to oppose the influence of peripheral vascular resistance toward diminishing blood flow during hypertension There is some indication of this in the results of Landis Montgomery and Sparkman and of Corcoran and Page who observed that in contrast with other pressor substances such as adrenalin and pitressin renal extracts can cause an equivalent and considerable rise in blood pressure without so contracting the peripheral vascular field as to lower

(6) J E pe Med 74 91 103 July 1 1941

blood pressure 5 34 mm Hg No difference could be demonstrated in the pressor activity of extracts of normal kidneys and of those from persons with glomerulonephritis and benign hypertension Neither could any quantitative relationship be demonstrated between the height of the patients blood pressures during life and the pressor activity of their respective heated kidney extracts

Injection of human kidney extract into each nephrectomized rabbit was followed 10 minutes later by injection of a standard dose of heated rabbit kidney extract to detect the presence of protective or antipressor effect in the human kidney extracts Extracts from three normal kidneys strikingly reduced the effect of subsequent injections of rabbit renin but the remainder had little or no effect The average protection afforded by extracts from kidneys of hypertensive persons showed similar wide variation and was only slightly less than that accorded by normal extracts There was no consistently inverse relation between pressor activity and protective action

Finally to test the nature of the pressor substance in human kidney extracts 10 samples which elevated the blood pressure of anesthetized nephrectomized rabbits by 10 to 34 mm Hg were injected also into unanesthetized rabbits Five of these extracts though pressor for nephrectomized rabbits had no effect on unanesthetized rabbits presumably because of the protective action of normal functioning kidneys The other five however elevated blood pressure 5 25 mm Hg without diminishing peripheral blood flow The effects of these few active human kidney extracts were therefore similar to those of renin as observed previously for heated rabbit kidney extracts and in the renin activator angiotonin system described by Page

Present methods while yielding suggestive results seemingly do not demonstrate any clear relation between blood pressure during life and the renin content of kidney tissue after death This conclusion does not

DISEASES *of the* HEART *and* BLOOD VESSELS

WILLIAM D STROUD MD

skin temperature In these circumstances blood flow is undiminished

The results therefore indicate that the 'pressor effects of renal pressor substances are not due solely to vasoconstriction but include direct stimulation of the myocardium with increase in force or amplitude of ventricular systole Unless like the direct action of digitalis on the normal heart this action of renin or angiotonin leads to diminution of ventricular volume below optimal size the effect will be to increase cardiac output The fact that considerable rise in blood pressure may result without commensurate vasoconstriction may rest on these phenomena Potentiated perhaps by increase in tone of the large arteries and arterioles even without diminution of their caliber these effects may provoke the condition essential to arterial hypertension the achievement of a state in which the amount of blood contained within the systemic arterial tree is increased in relation to the capacity of this arterial system

DISEASES *of the* HEART *and* BLOOD VESSELS

WILLIAM D STROUD M D

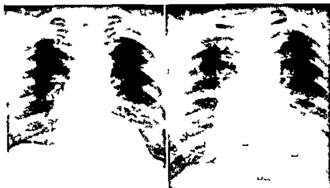
PART IV

DISEASES OF THE HEART AND BLOOD VESSELS

ETIOLOGIC DIAGNOSIS

Arteriosclerosis

Arteriosclerotic Heart Disease Arthur N Ferguson[1] (Ft Wayne) discusses etiology pathology symptoms complications treatment and prognosis in this condi



F g 71 (l ft) —C 2 F lm t k S ptemb 1938 H t n mal
F g 2 (ght) —S m S ptemb 1940 Enl g m t f h t

tion and presents six cases in detail one of which is given here as belonging to the group with heart failure

Man 66 in September 1938 after complete physical examination which showed no symptoms referable to the heart complained of some dizzines probably due to cerebral arteriosclerosis The heart was normal in size with clear tones Blood pressure was 162/96 and pulse 64 and regular Examination of eyegrounds revealed moderate arteriosclerosis

(1) J I d M A 35 129 139 M h 194

X ray study showed a normal heart (Fig 71) An electro cardiographic tracing was normal Diagnosis of generalized arteriosclerosis was made

In November 1939 the patient returned for another yearly physical examination He had been in rather good health until a cold developed 10 days before examination Again the heart was normal in size with clear tones Blood pressure was 158/94 X ray examination revealed the heart normal Comparison of a new electrocardiographic tracing with the one made a year earlier showed that the T wave in the second

Fig 3 —S me ca e a p ed ng Ele trocard gram sh wing le d I ly n th su ce ars P g ssi e lower g f T w ve

tracing was lower in amplitude Diagnosis was early coronary arteriosclerosis and he was advised to reduce his activities He returned in September 1940 for another yearly check up He had not been feeling well complaining of shortness of breath particularly at night which interfered with sleep Examination showed some enlargement of the heart, with clear tones Blood pressure was 142/98 Some moist rales were present in the base of both lungs and the liver was 2 fingerbreadths lower Obviously early heart failure was present X ray confirmed the enlarged heart (Fig 72) An electrocardiogram showed that the T wave had practically disappeared in lead I, so that it was almost isoelectric (Fig 73) which is definite electrocardiographic evidence of coronary arteriosclerosis Treatment consisted of cessation of work bed rest after meals 10 hours in bed each n digitalis aminophylline and vitamin B Thy

able improvement, and signs of heart failure disappeared He continued however to rest and to take medication

[If the patient had been digitalized in November 19 9 would congestive failure have been prevented for a number of years?—Ed]

Arteriosclerotic Heart Disease Robert S Berghoff (Loyola Univ Chicago) states that this condition is not a disease but merely part of the process of growing old thus prognosis is promising Concerning drugs in treatment digitalis in small and sustained doses leads not only to a real amphoria but to distinct im provement elimination of symptoms and prolongation of a useful existence Heredity is an important factor in etiology and excesses of all kinds physical mental gastro intestinal alcoholic and with tobacco are dis tinctly relatively important Moderation of activities and reduction in pace of living are required to reach old age

[I agree on the heredity but a far as I know no one has proved that excesses of all kinds phys cal mental gastro intes tinal alcoholic and with tobacco are distinctly relatively impor tant —Ed.]

Distribution of Iodine in the Wall of Normal and Sclerotic Arteries Ehrlich first pointed out that drugs are not equally distributed in the organs of the body Iodine has been used empirically for many years in treatment of arteriosclerotics In an experi mental study P Masson[3] produced arteriosclerosis in four rabbits by feeding cholesterol dissolved in oil Five rabbits were kept as controls All were given 0 2 Gm potassium iodide daily for nine days after which they were killed and the aorta was studied for iodine content Those aortas that showed absence of arterio-sclerotic changes contained either no iodine or only a small amount of it Iodine was found in the aortas of all the rabbits that had been treated with cholesterol and with the exception of a mild instance of sclerosis the iodine content was definitely greater than the max imum found in the controls It is therefore concluded

that deposition of iodine in the aorta may be obtained and that the sclerotic aorta shows a special affinity to iodine

Bacterial Infection

Circulatory Failure in Acute Infections Richard V Ebert and Eugene A Stead Jr[4] (Harvard Univ) describe the changes in circulation which occur in so-called medical shock produced by certain acute infections and consider whether a diminished blood volume or venous pooling is the primary factor in the production of this type of circulatory failure Eight patients with circulatory failure produced by acute infection were studied There were five with lobar pneumonia four of whom had bacteremia There was one with streptococcic septicemia one with staphylococcic septicemia and one with bronchopneumonia without bacteremia The circulatory failure was characterized by a decrease in peripheral blood flow and a fall in arterial pressure

Circulatory failure in these cases does not have the same mechanism as that of hemorrhage or traumatic shock because the plasma volume is not decreased and transfusions are not beneficial It is not caused by venous pooling because filling the venous system does not improve the circulation The entire cardiovascular system appears to be damaged by the infection The absence of congestion and the fact that venous pressure is not increased may be explained by simultaneous injury to the heart and loss of venous tone Improvement in the circulation occurs only when the infection is brought under control Therapy should therefore be directed toward overcoming the infection rather than attempting to treat the circulatory failure itself

Results of Chemotherapy in Subacute Bacterial Endocarditis Henry Field Jr (Univ of Michigan) Sibley W Hoobler (Peter Bent Brigham Hosp) and Noyes L Avery, Jr[6] (Univ of Michigan) report on 36 pa

(4) J Clin Investigation 20 671-679 November 1941
(6) Am J M Sc 202 793-803 December 1941

tients treated with sulfonamide drugs Five patients had one or more probably falsely negative blood cultures three had probable sterilization of the blood stream with normal temperature temporarily and one—a probably proved case—was cured Several patients received more than one sulfonamide 23 received sulfapyridine 13 sulfanilamide 7 sulfathiazole 4 sulfamethylthiazole 1 neoprontosil and 1 sodium paranitrobenzoate Of five patients who also received continuous intravenous infusion of heparin one died of cerebral hemorrhage and none was cured

These experiences with chemotherapy of subacute bacterial endocarditis warrant persistence in the accumulation of data concerning the different adjuncts to chemotherapy and the selection of a sulfonamide drug on the basis of bacteriostasis demonstrable in vivo for the strain of organism obtained from the individual patient

[This is an important contribution We have not seen a patient definitely cured with any of the sulfonamides used with or without heparin hypertherm or arsenic preparations—Ed]

Heparin in Subacute Bacterial Endocarditis Jay McLean B B M Meyer and J M Griffith (Columbus O) report two cases in detail and review 67 cases reported in the literature They conclude that the results obtained do not warrant further trial of treatment by heparin according to the plan used Incidence of subarachnoid and cerebral hemorrhage was alarming Authorities like Friedman Fletcher and Blumer recommend that the method be abandoned The plan of subjecting a patient to the effects of heparin sulfapyridine and a large quantity of fluid simultaneously all within two weeks appears injudicious on the basis of experience not only in regard to prevention of postoperative thrombosis but in regard to healing quantity of fluids which must be administered to patients with badly damaged hearts and possibly diminished kidney function and the vomiting accompanying simultaneous administration of sulfonamides

If heparin treatment is to be continued the authors believe that the various factors which must be considered before treatment is given as well as be controlled during treatment will require the cooperation and facilities afforded by a group of scientists working in an institute for medical research which could admit an adequate number of selected patients for a suitable duration

Congenital Anomaly

Tetralogy of Fallot Contrast Visualization of Heart and Great Vessels A Grishman M F Steinberg and M L Sussman[8] (New York City) point out that since the work of Robb and Steinberg on contrast visualization of the cardiac chambers, it has been suspected that an important practical application of this method would be found The authors report a case of tetralogy of Fallot in which contrast visualization established the pathologic physiology

Man, 26 has been under observation in the cardiac clinic of Mount Sinai Hospital since birth He has always been cyanotic and clubbing of the fingers has been noted since he was first admitted A loud systolic murmur, heard best over the pulmonic area but also present over the entire precordium was evident X ray examination revealed slight enlargement of the heart to the left Electrocardiographic examination showed a regular sinus rhythm, no axis deviation and a notched P wave in lead II No other abnormalities were noted The clinical diagnosis was congenital heart disease patent intraventricular septum and pulmonic valve tenosis

The patient was active and without discomfort until March 1938 He was then hospitalized because of pain in the lower right side of the chest and dyspnea This proved due to a spontaneous pneumothorax which completely resorbed in 10 days

Circulation studies revealed vital capacity 3 500 cc blood pressure, 110/80 venous pressure 6 5 cm saccharin time 12 seconds, and ether time 12 seconds At 11 seconds the patient complained of a generalized pinching or pins and needles' sensation beginning in the neck and head and then in the upper extremities and chest This was followed by similar phenomena in the lower trunk and extremities These were interpreted as due to a venous arterial shunt

(8) F d 1 gy 3 1 8 180 Aug t, 1941

In September 1939 a contrast visualization made by the original method of Robb and Steinberg demonstrated enlargement of the right and left ventricles The pulmonary artery did not appear to be enlarged Although there seemed

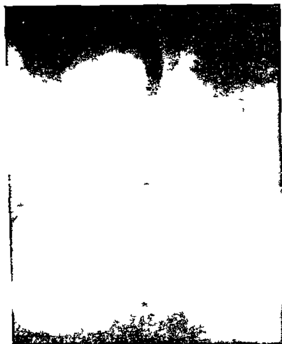


Fig 74 — V l t f ght al f h t, ¾ ft i j t F lm m d l ft t bl d l t n

to be simultaneous visualization of the pulmonary artery and aorta the demonstration was not conclusive

In May 1940 the examination was repeated using both the moving picture and the fluorographic multiple exposure technics with diodrast These demonstrated hypertrophy and dilatation of the right ventricle stenosis of the pulmonary artery above the conus an intraventricular septal defect below the origin of the pulmonary artery with a right-to left shunt The aorta left ventricle and pulmonary artery were opacified during the same systole The left ventricle remained visualized long after the other parts of the heart and the

great vessels Its lumen was much smaller than that of the right ventricle There was no definite outflow tract from the left ventricle other than through the septal defect Backflow of the opacified blood *into the vena cava inferior* and the hepatic veins was noted, suggesting insufficiency of the tricuspid valve

These observations confirm the diagnosis of tetralogy of Fallot Complete dextroposition of the aorta (absent aortic conus) can be assumed and the case classified as type II (Spitzer) or partial *transposition* (Rokitansky) Absence of right axis deviation in the electrocardiogram suggests complete transposition of the aorta which gives rise functionally to a *cor biatriatum monoventriculare* In this way the prolonged opacification, for ever 10 seconds of the left ventricle is explained when the pulmonary artery and aorta emptied in *the normal periods* of four and three seconds respectively It is assumed that the left ventricle emptied only through the septal defect presumably by eddy currents

Fig —Diagram of film in Figure 74 1 Superior ... 2 Right ... appendage 3 Inflow tract, right ... 4 Outflow tract, right ... 5 Pulmonic conus and ... 6 Hepatic vein

Congenital Heart Disease during Pregnancy Curtis L Mendelson and Harold E B Pardee[9] state that since 1932 there have been 1 089 cases of organic heart disease in approximately 31 000 obstetric patients at the New

York Lying in Hospital Of these 1 069 cases 20 were diagnosed as cases of congenital heart disease In eight of these cases pulmonic stenosis was the sole discharge diagnosis The patients presented a common clinical picture indicating a congenital lesion which differed from the other diagnostic groups All had a loud systolic murmur and most of them a thrill over the pulmonic area There were varying degrees of enlargement of the heart and of the pulmonary conus It is probable that other lesions were present and possibly the tetralogy of Fallot in most of them with its association of pulmonic stenosis dextroposition of the aorta patent interventricular septum and right ventricular hypertrophy

RELATION OF PARITY AND CARDIAC FUNCTIONAL CAPACITY

	CLASS 1	CLASS 2	CLASS 3	CLASS 4
Total no of patients	7	9	3	1
Primigravidas	4	4	3	0
Multigravidas	3	5	0	1

The cardiac functional capacity of the 20 patients in the present series according to the scheme of the New York Health Association is seen in the table Thus 80 per cent of patients were in classes 1 or 2 Except for one case of cardiac failure there was no change in functional capacity during pregnancy labor or the puerperium

EFFORT SYNDROME

Neurocirculatory Asthenia (Da Costa s Syndrome Effort Syndrome Irritable Heart of Soldiers) Paul D White[1] (Boston) defines the condition as characterized by dyspnea (often with sighing respiration) palpitation precordial pain exhaustion dizziness nervousness and sometimes tremor sweating headache and syncope aggravated by effort or excitement and attending or following infection or physical or nervous strain especially in hypersensitive individuals who in extreme cases may show the condition more or less constantly with little or no provocation It is probably not a specific

(1) Mod C pt C d scul D V 3 11 8 August, 194

disease It may occur either alone, i e as the only manifestation of ill health, or it may complicate almost any disease including structural heart disease and psychoses or other diseases of the circulatory or nervous systems It is not very common in civilian life in 3 000 persons there was an incidence of 12 per cent in 503 of whom the condition was uncomplicated by heart disease and in 62 the condition was superimposed on heart disease In wartime incidence varies greatly from a very few cases among soldiers in training to a considerable number under the strain of severe combat In the British army in World War I not less than 44 000 soldiers with effort syndrome became pensioners A more careful preliminary examination to exclude persons with or prone to higher grades of the disorder may result in a decrease

Women are somewhat more prone than males to develop neurocirculatory asthenia but the special strains on the soldier *in combat* result in a considerable preponderance of males with this condition in wartime Proverbially the condition is most common in young adults but that may be in part because such persons will not or cannot avoid factors of strain which precipitate the condition One of the most definite etiologic relations of neurocirculatory asthenia is that of heredity There is a history of considerable incidence of nervous and psychic disorders and of the syndrome itself in ancestors and contemporary relatives The condition is more common in those of slight physical build with long chests and ght hearts It may occur in any occupa demanding prolonged concen

seconds respectively It ious attention are more com tricle emptied only thoroughly when physical

although there are often tachycardia with flushing and dermatographism cold moist hands excessive sweating and sometimes slight elevation of blood pressure The heart itself is structurally normal without important murmurs

Concerning course and prognosis the condition may last from hours to a lifetime A long life with variable degrees of recurrent trouble from this bothersome condition is to be expected in the average case There are four principles of treatment and prevention (1) reassurance about the heart itself and any other serious disease or shortening of life (2) resignation of the individual to this liability if he has a considerable degree of neurocirculatory asthenia with relatively little provocation but not adoption of a state of invalidism (3) rest physical and mental for an acute occurrence or recurrence and avoidance of similar strain in the future so far as possible and (4) reeducation with adoption of a physical and mental program of a useful and happy life which will minimize symptoms of neurocirculatory asthenia Late hours tiring contact with crowds of people hard work without frequent relaxation or holidays excessive use of tobacco alcohol tea and coffee are largely to be avoided

[It is unfortunate that this syndrome has previously in the main been considered a cardiovascular rather than a neuropsychiatric problem —Ed]

Hypertension

Accuracy of Clinical Measurements of Arterial Blood Pressure Charles Ragan and James Bordley III advocate that the routine clinical method of measuring blood pressure should not be looked on as truly

disease It may occur either alone i e, as the only manifestation of ill health, or it may complicate almost any disease including structural heart disease and p r choses or other diseases of the circulatory or nervous systems It is not very common in civilian life, in 3 000 persons there was an incidence of 12 per cent, in 303 of whom the condition was uncomplicated by heart disease and in 62 the condition was superimposed on heart dis ease In wartime incidence varies greatly from a very few cases among soldiers in training to a considerable number under the strain of severe combat In the Brit ish army in World War I not less than 44 000 soldiers with effort syndrome became pensioners A more careful preliminary examination to exclude persons with or prone to higher grades of the disorder may result in a decrease

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race since neither group is a true race and thorough studies will be required to determine the etiologic factors for the differences

Blood Pressure Studies in the Aged Isidore Miller[4] (New York City) points out that 260 of every 1 000 persons in the United States are 40 and over It is estimated that by 1960 36 per cent of the population will be between 40 and 65 In 1930 there were 6 500 000 persons in this country 65 and over by 1980 it is estimated that there will be 22 000 000

EFFECT OF AGE ON THE AVERAGE BLOOD PRESSURE

Years	Men			Women		
	Systolic	Diastolic	Pulse	Systolic	Diastolic	Pulse
50–54	132	86	46	155	94	61
55–59	137	87	50	154	87	67
60–64	142	86	56	156	84	72
65–69	146	84	62	174	93	81
70–74	148	84	64	161	88	73
75–79	154	84	0	165	90	75
80–84	154	85	69	176	94	82
85–89	157	86	71	145	83	62
90–94				158	75	83

Life insurance tables of normal blood pressures for white males show that the pressure rises from 120 systolic and 79 diastolic at 20 to 138 systolic and 89 diastolic at 65 For a general rule *permitting variations* of 10 mm in systolic and 5 mm in diastolic pressure the normal range is 110 148 systolic and 70 95 diastolic approaching the upper limits in the older age groups

Hypertensive Heart Disease of 10 to 20 Years Duration Nathan Flaxman[5] (Loyola Univ Chicago) states that recent optimistic reports on the results obtained with so called specific surgical treatment for essential hypertension have failed to account for the fact that many hypertensive patients live for years without such

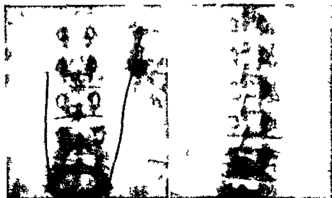
(4) New York St J Med 41 1631 1635 A 15 1941
(5) A I t M d 15 821 8 8 November 1941

the clinical estimate of the systolic pressure is likely to be too low if the arm is large the clinical estimate of both systolic and diastolic pressure is likely to be too high The error in either direction may exceed 30 mm Hg These facts must be remembered whenever it is necessary to make a decision concerning the diagnostic or prognostic significance of minor depressions or elevations in the level of the blood pressure Statistical studies of the relation between blood pressure and body weight should take into account the influence of the circumference of the arm on the accuracy of the blood pressure measurements

Blood Pressure Studies on West Indians and Panamanians Living on the Isthmus of Panama B H Kean[3] (Ancon, Canal Zone) presents studies which indicate that the incidence of high blood pressure is much greater in West Indians than in Panamanians and that the incidence of low blood pressure is much greater in the latter than in the former The standards used in determining presence of hypertension were high a systolic blood pressure of 150 mm is certainly abnormal under conditions of rest If 140 mm had been used, the incidence of hypertension would have been higher in both groups but the ratios would not have been altered Reaction of the West Indians and their descendants to a strange environment might have been responsible for the hypertension but Phillips reports indicate that the Negroes in Jamaica have a high incidence of hypertension The high incidence of hypotension in Panamanians may possibly indicate that levels of normal blood pressure must be revised downward The evidence that hypotension is a disease or an important sign of one except in rare conditions has never been convincing and it is Kean s impression that hypotension is normal tension in Panama and elsewhere The difference in arterial tension between the two groups cannot as yet be attributed to the difference in

(3) Arch Int Med 68 466 475 Sept mbe 1941

usually considered to be dependent on hypertension has been found in 113 The authors conclude that organic renal disease is a common occurrence in cases of so called essential hypertension Examination of the genito urinary tract for abnormalities is an important part of the study of these cases A history of renal dis



Fg 8 (l ft) —R t gr d [y l g m b l t l hyd ph a.
Fg 9 (ght) —Py l m ft t j t n f t t m d um m ked n l pt

ease often antedates onset of arterial hypertension even when no abnormality can be found There is justification for regarding the condition in these cases not as essential hypertension but as a different disease

Retinal Arteriovenous Nicking Relation to Enlargement of the Heart in Ambulatory Patients with Hypertension Samuel Shelburne J Leeper Hawley and A S McGee[7] (Baylor Univ) found in 317 patients with hypertension that retinal arteriovenous nicking is so closely related to enlargement of the heart that if nicking is found an enlarged heart may be expected If this lesion is found in a patient with enlargement of the heart the latter condition can be accounted for by hypertension even if blood pressure is normal at examination If the heart of a hypertensive patient

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operations Flaxman reports 11 cases in which patients with hypertensive heart disease lived from 10 to 20 years (average 13 7 years) after onset of cardiac symptoms

DURATION OF HYPERTENSIVE HEART DISEASE

YEARS	NO OF PATIENTS	PER CENT
10	2	18 2
11	1	9 1
12	4	36 3
15	1	9 1
16	1	9 1
19	1	9 1
20	1	9 1
Av 13 7 yr		

[I still feel that surgical treatment for essential hypertension is seldom indicated —Ed.]

Studies on Essential Hypertension Henry A Schroeder and J Murray Steele[6] (New York City) review 200 cases of so called essential hypertension with



Fig. 6 (left) —Retr gr de py l gr m Sm ll fill g defe t in m ddle calix of f nct l left k d ey

F 7 (r ght) —R t og ade py l gram, h wing d t rt of r ght r al pel with gul t on f ete t u t r pel ic jun ti n

a view to ascertaining the presence of organic renal disease The genito-urinary tract was especially studied in 178 cases Evidence of renal disease of a nature not

(6) Arch Int Med 68 61 93 A gu t, 1941

nephritis associated with late hypertension and chronic glomerulonephritis The importance of careful observation of the changes in the retinal vessels and the necessity for more accurate observation are emphasized *There are many* reports *in the* literature in which retinal arteriosclerosis is evaluated as 4 plus or grade 3 but the lesions are not described Such a notation is meaningless It is much more valuable to state whether arteriovenous nicking extremely narrow arteries changes in the caliber in arteries and the like are present

TABLE 1 —INCIDENCE OF ARTERIOVENOUS NICKING WITH AND WITHOUT ASSOCIATED ENLARGEMENT OF THE HEART*

	No PATIENTS	%
Nicking present heart enlarged	142	95 7
Nicking present heart normal in size	6	4 3

Th t f l g m t w dioth tio f 50 pe t o b h t d m t 10 pe t b th p d t d di g to tabl f H dges d Ey ter

TABLE 2 —RELATION OF ABSENCE OF ARTERIOVENOUS NICKING TO ENLARGEMENT OF THE HEART

	N PATIENTS	%
Nicking absent heart enlarged	23	31
Nicking absent, heart normal in size	51	69

Th t n f nl g m t w ca d th c t f 50 p c t b a h t d m t 10 pe t b e th p d t d o d g t t bl f Hodg d Ey te

Interpretation of Blood Pressure Behavior during Pregnancy and the Puerperium R A Bartholomew and E D Colvin[8] (Atlanta Ga) place particular emphasis on the value of retinal examination in the differentiation and management of true toxemia and vascular disease and the importance of examination of the formalin fixed placenta in the final classification of the disorder When the patient presents herself in the first trimester of pregnancy if she is an adolescent one may anticipate a greater likelihood of hypertension of a truly toxic nature late in pregnancy Likewise if the patient presents certain stigmas of glandular disease as noted by Vorzeimer and associates such as disturbance

(8) Am J Ob t & Gy 4 646 655 O t be 1941

is *enlarged* and no arteriovenous nicking *is found*, the enlargement is not likely to be due to hypertension alone and a careful search for other lesions such as those of severe coronary arterial disease syphilis or rheumatic fever is clearly indicated

There is apparently no relation between the early change in the retinal arteries which has been designated

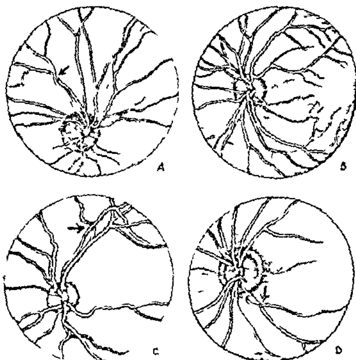


Fig 80 —Degree f art r o n k g A d S le B, non (normal) r t l arte nd) C ly nd D mod at

early arteriovenous nicking and enlargement of the heart, but the later change called moderate arteriovenous nicking is definitely related to enlargement of the heart though not as closely as the fully developed lesion (definite arteriovenous nicking) Arteriovenous nicking is important in differentiation of the chronic

tiated not only by the clinical course but by retinal examination Final proof rests on examination of the formalin fixed placenta

DATA ON RETINAL EXAMINATION EARLY AND LATE IN PREGNANCY IN 286 CONSECUTIVE CASES

No of patients showing normal A V ratio (2–3)	239 (83 6%)
No maintaining normal blood pressure to term (diastolic pressure not above 80 mm Hg)	179 (74 9%)
No developing hypertension 4–6 wk before term (diastolic pressure above 80 mm Hg)	60 (25 1%)
No showing apparent change from normal A V ratio to between 1–2 and 2–3 during pregnancy (vascular disease?)	9 (15 0%)
No with proved true toxemia (arterial spasms and toxic infarcts)	22 (36 7%)
No with presumably mild toxemia (retinal and placental examination either negative or not done)	29 (48 3%)
No of patients showing disturbed A V ratio between 1–2 and 2–3 occasionally 1–2 seldom 1–3	47 (16 4%)
No maintaining normal blood pressure to term	17 (36 2%)
No developing hypertension 4–6 wk before term	30 (63 8%)
No with proved vascular disease (absence of arterial spasms and toxic infarcts)	6 (86 7%)
No with proved true toxemia (presence of arterial spasms and toxic infarcts)	4 (13 3%)

S ty f pe t f p t t w u d 30 d 86 p t h dd t h tl d p d 0 mm Hg

Effect of Parity on Average Blood Pressure and on Incidence of Hypertension C E Isenhour K Kuder and L V Dill[9] (Cornell Univ) determined the incidence of hypertension and the average blood pressure in women of varying age groups with and without children and the relation to the toxemias of pregnancy

(9) Am J M S 03 3 3 340 M h 194

in height weight ratio hypothyroidism pituitary dis orders etc she is more likely to develop true toxemia of pregnancy

The authors consider 80 mm Hg the upper limit of normal diastolic blood pressure during pregnancy and the puerperium and any rise above this figure indicative of hypertension While there is usually a corresponding rise in systolic blood pressure, the latter is subject to more variations and is not so reliable an index Considering the fact that most diastolic blood pressures range from 60 to 70 mm Hg throughout pregnancy any rise above 80 mm is a danger signal and necessitates observation at five to seven day intervals to avoid overlooking a rapidly progressing true toxemia

Two thirds of patients showing mild to moderate disturbance in A V ratio of the retinal vessels early in pregnancy develop mild to moderate hypertension and albuminuria four to six weeks before term This behavior is on the basis of vascular disease progresses slowly and seldom requires interruption of pregnancy

The greater the disturbance in A V ratio and the more marked the increase in arterial light reflex and A V compressions the greater the hypertension and the earlier in pregnancy it arises Only one fourth of patients showing normal A V ratio early in pregnancy develop hypertension and albuminuria four to six weeks before term True toxemia is relatively greater in this group than in the group with disturbed ratios. Hypertension due to vascular disease is accompanied by less edema headache albuminuria and blood uric acid increase and is more responsive to rest in bed than that of true toxemia

Arterial spasms indicate true toxemia If they are found together with a disturbed A V ratio increased light reflex and A V compression they indicate true toxemia superimposed on vascular disease Hypertension due to toxic types of placental infarcts may simulate that due to vascular disease It can be differen

tiated not only by the clinical course but by retinal examination Final proof rests on examination of the formalin fixed placenta

DATA ON RETINAL EXAMINATION EARLY AND LATE IN PREGNANCY IN [illegible]80 CONSECUTIVE CASES

No of patients showing normal A V ratio (2–3)		[illegible]9 (83 6%)
No maintaining normal blood pressure to term (diastolic pressure not above 80 mm Hg)	1[illegible]9 (74 9%)	
No developing hypertension 4–6 wk before term (diastolic pressure above [illegible]0 mm Hg)	60 (2[illegible] 1%)	
No showing apparent change from normal A V ratio to be *tween 1–2 and 2–3 during* pregnancy (vascular disease?)	9 (15 0%)	
No with proved true toxemia (arterial spasms and toxic infarcts)	22 (36 7%)	
No with presumably mild toxemia (retinal and placental examination either negative or not done)	29 (48 3%)	
No of patients showing disturbed A V ratio between 1–2 and 2–3 occasionally 1–2 seldom 1–3		47 (16 4[illegible])
No maintaining normal blood pressure to term	17 (6 %)	
No developing hypertension 4–6 wk before term	[illegible]0 (63 8[illegible])	
No with proved vascular disease (absence of arterial spasms and toxic infarcts)	26 (86 [illegible]%)	
No with proved true toxemia (presence of arterial spasms and toxic infarcts)	4 (13 3%)	

Sixty f pe t f p t t w nd 0 d 86 pe t h w d d ast h bl d p und 0 mm Hg

Effect of Parity on Average Blood Pressure and on Incidence of Hypertension C E Isenhour & Kuder and L V Dill[9] (Cornell Univ) determined the incidence of hypertension and the average blood pressure in women of varying age groups with and without children and the relation to the toxemias of pregnancy

(9) Am. J M S 03 33 340 M h 194

A slightly higher systolic level was found to be maintained by the parous woman than by the nulliparous at all ages save the 20 29 age group, where there is a slight

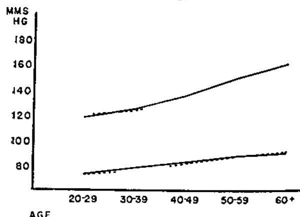


Fig 81 —A age sy tcl c a d d tol c pr u fo pa o (sol d l e) and null p u (d tted l n) omen cco d ng to age gr ups

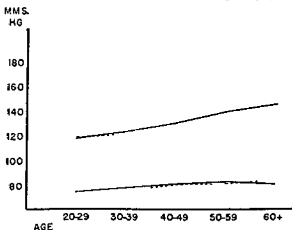


Fig 82 —Ave ge sy t l c a d d t l c pressures f pa o (ol d l e) a d null pa ous (dotted l) om n f llow g moval f all hyp rt e ca

ly lower level There was no consistent difference in the diastolic level save in the 30 39 group where the parous group showed a minimally higher level (Fig

81) Following removal of all hypertensive patients from the entire group the average systolic pressure still showed a slightly higher range in the parous patient while the diastolic remained essentially the same (Fig 82) This suggests that the hypertensive patients present in each group were relatively equal in number and in degree of hypertension and that the slightly higher level of systolic pressure among the parous women was not caused by inclusion of a number of hypertensive patients

Since no demonstrable difference could be noted in the incidence of hypertension and the average blood pressure levels of parous and nulliparous women the authors conclude that the hypertension and hypertension producing diseases which occur following many of the toxemias of pregnancy are probably not the result of this complication of pregnancy but occur usually if not always in patients whose vascular systems are endowed with the tendency to hypertensive disease

[This conclusion confirms the present conception that heredity plays a most important r le in the development of hypertens on —Ed.]

Study of 104 Cases of Uterine Fibroids Associated with Arterial Hypertension Discussions of uterine fibroids and arterial hypertension have been periodic in the literature since 1885 but many questions are not settled The association presents a far more complex problem than hypertension alone W O Johnson[1] (Univ of Louisville) reports a study in which 104 patients were observed from two to eight years after operation All patients had an admission blood pressure of 165/85 or higher The series was followed closely to ascertain whether the surgical risk taken in these severely handicapped patients was justified and their salvage was satisfactory Most patients were on relief or completely incapacitated because of the fibroids or the combination of fibroids and myocardial failure Obesity was a complication in most cases Fifty five were 40 or younger the oldest was 69 All had been

(1) Am J Ob t & Gyn 43 231 245 F bru ry 194

A slightly higher systolic level was found to be maintained by the parous woman than by the nulliparous at all ages save the 20 29 age group where there is a slight

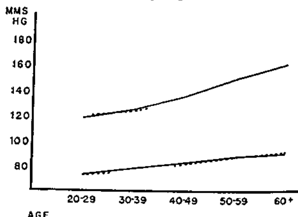
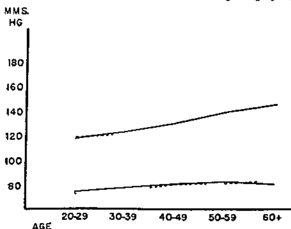


Fig 81 —A ge sy t l c a d d st l c pres u fo pa ou (sol d l e) nd null pa ou (dott d l e) men c d ng to age groups



F g 8 —A e ag y tol d diast l c p essu es f r parous (ol d l ne) a d n ll pa us (d tt d l ne) w m n f ll w ng rem l f ll hyp t e s

ly lower level There was no consistent difference in the diastolic level save in the 30 39 group where the parous group showed a minimally higher level (Fig

mortality of 19 2 per cent On the whole a debilitated greatly handicapped group of women has been restored to greater capacity In the white patient group 50 per cent are working and 50 per cent are on relief but comfortable and able to be about better than before operation In the colored group 65 are working and apparently well for years and 19 are on relief and definitely subjectively relieved Some are incapacitated by progression of the heart condition in only three of these is the condition apparently hopeless Thus the results in this series show that if these cases are properly handled mortality is no greater despite the arterial hypertension than for the average major pelvic operations for that age grouping

Results of Sulfocyanate Therapy in Hypertension *Chester M Kurtz Herman H Shapiro and C Selby* Mills[3] (Univ of Wisconsin) during the past 11 years treated 50 patients with essential hypertension with potassium sulfocyanate Barker s method of laboratory control was used routinely since 1935

Subjective improvement as estimated by disappearance of headaches dizziness tinnitus etc was definite in 63 per cent fair in 20 and disappointing in 17 Six patients had poor tolerance for cyanate as shown by *precordial pain in one skin rash in three and skin rash* combined with falling hair in two There were two other patients who felt distinctly worse under treatment Some degree of reduction of blood pressure was obtained in every case Objective results were satisfactory in 78 per cent fair in 16 and poor in 6 Average systolic pressure for the entire group dropped from 197 before treatment to 156 with treatment while average diastolic pressure dropped from 115 to 94 In four cases the blood *pressure remained normal for* months or years after discontinuing thiocyanate The optimal blood cyanate level ranged from 4 to 16 mg per 100 cc with an average of 8 3 mg Maintenance dose of potassium sulfocyanate varied from 3 to 21 five-grain doses per week

(3) Am J M S 0 3 8 9 S ptemb 1941

pregnant with a total of 100 living children in contradiction to the assumptions that women with fibroids are infertile and that women who do not become pregnant develop fibroids Dominant cause of incapacitation was pain vaginal bleeding was the next symptom of importance and other complaints were weakness shortness of breath and edema of the ankles, associated more with the anemia or cardiac disturbances than with the mechanics of pelvic pathology Fifty patients had a diagnosis of cardiovascular disease on initial examination and in some cases there had been eight years of previous medical treatment for a heart condition

CAUSES OF DEATH

UNDER 40 YEARS	OVER 40 YEARS
Hospital deaths 1 Nephritis and uremia	Hospital deaths 1 Bronchopneumonia 1 Nephritic toxemia 1 Pulmonary edema (? uk secondary closure)
Under 1 year 1 Heart failure Under 2 years 1 Cardiovascular disease	Under 1 year 1 Cardiovascular disease 1 Myocarditis 1 Heart failure 1 Lobar pneumonia 1 Cancer fundus uteri
2–6 years 1 Cardiovascular disease 1 Pulmonary tuberculosis 1 Stab wound shoulder pneumonia 1 (White) Cardiovascular disease	2–6 years 1 Heart failure 1 Stroke 1 Cerebral hemorrhage 1 Fracture of vertebra cord lesion 1 Carcinoma cervix

Average time of operation in all cases was 1 hour and 40 minutes The patients were conditioned for an average of 10 days before operation low spinal anesthesia was given A disturbing factor was the marked drop in blood pressure which could not be controlled despite careful preparation and low spinal anesthesia with small doses Disturbance in urinary output also occurred Causes of death are given in the table There was a hospital death rate of 3 8 per cent and a total eight year

permanent result of operation the patient s blood pressure must be observed for at least two years In a group of cases of hypertension in which the patients are carefully selected for renal operation the number of cases in which blood pressure will be restored to normal and remain so for a year or more after operation unfortunately will be small Even so one patient whose blood pressure is restored to normal by renal operation would justify a vast amount of clinical search and investigation It is difficult to find patients who are more appreciative than patients apparently cured by this procedure

Total Thoracic and Partial to Total Lumbar Sympathectomy and Celiac Ganglionectomy in Treatment of Hypertension Keith S Grimson (Univ of Chicago) reports on studies in progress of the effect of extensive to total paravertebral sympathectomy in hypertension Several approaches to the sympathetic denervation of the splanchnic area have been reported Ventral rhizotomy consisting of intraspinal section of the lower six thoracic and first two lumbar anterior spinal nerve roots has been used in some cases Serious surgical complications forced abandonment of this procedure Subdiaphragmatic resection of the splanchnic nerves and part of the celiac ganglions together with resection of the first and second lumbar ganglions has been used by Adson and Allen in over 300 cases without an operative death Blood pressure reduction was good or fair in 31 per cent and temporary or poor in 69 per cent Supradiaphragmatic extrapleural splanchnicectomy consisting of resection of a long section of the greater splanchnic nerves above the diaphragm together with the tenth eleventh and twelfth thoracic ganglions the intervening sympathetic chain and the lesser splanchnic nerves has been used by Peet in more than 700 patients In 51 4 *per cent of 350 of these patients there was significant* blood pressure reduction Operation on many patients with advanced hypertension has given mortality of 3 4 per cent

(5) A S g 114 53 O I b 1911

with an average of nine doses weekly Extensive sympathectomy was done in two cases, but the results cannot as yet be evaluated

During the 11 years four patients died of heart failure four of cerebral hemorrhage one of coronary occlusion and two of pneumonia In no case could death be attributed either directly or indirectly to cyanate administration Thus the drug is regarded as a valuable aid in treatment of hypertension, capable of prolonging life and preventing disability when properly used It can be safely given provided laboratory control is exercised at all times

Surgical Kidney as Etiologic Factor in Hypertension William F Braasch[4] (Mayo Clinic) states that a unilateral non nephritic or 'surgical' kidney lesion is not a common cause of hypertension Records show that the incidence of such lesions in patients with hypertension who are amenable to operation is less than 1 per cent The renal lesion amenable to surgical treatment which occurs most often in association with hypertension is chronic unilateral pyelonephritis in either its diffuse atrophic or postoperative forms Acute cortical renal infection or perinephritic abscess seldom is a factor in causing hypertension Presence of renal stone or hydronephrosis will not affect blood pressure unless a secondary pathologic change in the renal tissue causes intrarenal vascular imbalance

In 17 cases with surgical operation on the kidney there was a postoperative drop in blood pressure but the hypertension returned within a few weeks or months after operation A temporary drop in blood pressure occurring immediately after operation often is caused by rest in bed and removal of a toxic irritant In several cases the blood pressure remained normal as long as two years after operation and then returned to the pre operative level In such cases it may be inferred that primary hypertension existed and had been temporarily increased by a surgical renal lesion To determine the

(4) Canad M A J 46 914 January 1942

sists in the experimental animal after total paraverte bral sympathectomy This observation demonstrates that the vascular bed is under an influence probably humoral the action of which is independent of the sympathetic nervous system If clinical hypertension were primarily

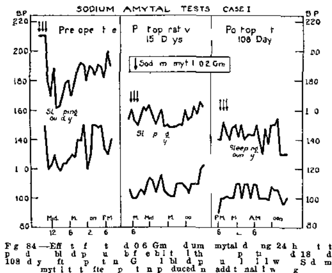


Fig 84—Eff t f t d 0 6 Gm d um mytal d ng 24 h t t p d bl d p u b f e bl t l th p t d 18 d 108 d y ft p t n G l bl d p u l l l w S d m myt l t t fte p t n p duced n add t nal l w g

renal in nature the large splanchnic vascular area de nervated by operation would also be under the same humoral vasoconstrictor influence

The possibility of improving the blood supply of the kidney and thus altering the formation of a renal pressor substance has been suggested by Peet Clinical studies of renal hemodynamics have however failed to show any consistent alteration following splanchnic area denervation in hypertensive patients The mechanism of hypertension in man is probably complex. It is gen erally accepted that it is mediated by increase of periph eral resistance offered by the vascular bed to blood flow The extent to which processes comparable to experimen tal renal or experimental neurogenic hypertension may

Celiac ganglionectomy and denervation of the periaortic complex of sympathetic nerves and ganglions has been carried out by Crile on 213 patients Transdiaphragmatic removal of the lower four thoracic and first or first and second lumbar sympathetic trunk ganglions

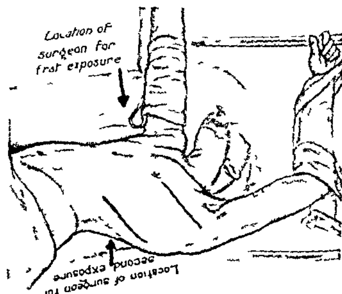


Fig 83 —P siti n dur ng tho ac c ope at on nd l cat on of two inc on used St llate and uppe e ght sympath t c gangl ns d ssected f ee th ough upp n s n and r m nd f th c trunk, planchnic erv cl a ganglion and t t mes first r fi t and se o d lumba gangl on removed th gh lower inc s on

together with a long segment of the splanchnic nerve has been used by Smithwick in many patients Emphasis is placed on the importance of the postoperative postural hypotension achieved

Thus although good results have been obtained, much has been left to be desired Clinical and symptomatic benefit appears more frequent than blood pressure decrease Studies of experimental renal hypertension of the type developed by Goldblatt and associates have offered little encouragement to sympathetic surgery in clinical hypertension This type of hypertension per

cavity is entered through the rib bed The free end of the sympathetic chain is picked up and its remaining portion and the splanchnic nerve and its connections are dissected free down to the diaphragm The pleura over the arch of the crux of the diaphragm is divided and the curved tip of the special round diaphragmatic retractor is placed in the arch Strong retraction on this instrument partly inverts the diaphragm and allows the celiac ganglion to be pulled up through the diaphragm by traction on the splanchnic nerve after blunt separation of the adjacent diaphragmatic muscle This ganglion is removed as completely as possible by dividing its distal connections The sympathetic chain is then followed down through the crux of the diaphragm as far as possible and divided The thoracic portions of the sympathetic trunk the splanchnic nerve and the celiac ganglion and occasionally also the first or the first and second lumbar ganglions are thus removed A medium sized pezzar catheter is then inserted into the pleural cavity through a stab wound between the seventh and the eighth rib in the midaxillary line and the incision is closed Air is evacuated from the thoracic cavity through the catheter and a negative pressure maintained for four or five days

Of 11 patients 8 had the thoracic procedures One died after the first stage and one after the second Three patients had both the thoracic and the abdominal procedure Some lowering of blood pressure has been observed in each patient No blood pressure lowering was observed after the first thoracic operation in nine patients Extensive cardiorenal studies on these patients before and after operations indicate that lowering of the pressure after extensive sympathectomy is due to a decrease in peripheral resistance

Surgical Approach to Hypertension Geza de Takats Howard E Heyer and Robert W Keeton[6] (Univ of Illinois) state that rest use of sedatives vasodilators toxic depressants and psychoanalytic sessions have never cured or arrested the progress of hypertension although their temporary palliative value especially in the early stages cannot be questioned Nevertheless after the age of 45 the death rate from hypertension is 4 times that from cancer and 20 times that from either tuberculosis or diabetes (Fig 55) The authors describe their classi

(6) J A M A 118 501 507 Feb 14 1942

play a role in man in increasing the peripheral resistance has not been clearly demonstrated Total paravertebral sympathectomy might accomplish more than splanchnic area denervation in treatment of hypertension in man, especially if there should be a component of a neurogenic nature in clinical hypertension Grimson therefore reports the development of a technic for total paravertebral sympathectomy which has been used in 11 patients with varying degrees of success

Technic—Operation is undertaken in three stages, two thoracic and one abdominal At each thoracic operation, the stellate ganglion and the entire thoracic sympathetic gangliated chain the entire length of the splanchnic nerve and its minor branches and the major portion of the celiac ganglion on that side are removed An effort is made, but without marked success to obtain through the diaphragm the first or first and second lumbar ganglions The third stage, if used, consists of bilateral excision of the remaining portions of the lumbar sympathetic chains down to or including the fifth lumbar ganglion The operation is of necessity transthoracic and transabdominal The thoracic stages are performed under ethylene anesthesia using positive pressure through a face mask and the abdominal operation under either spinal or ethylene ether anesthesia Long alligator forceps dissectors hooks and scissors both straight and curved, have been devised for dissection of the nerve roots and branches A special oval headed malleable retractor is used for the lungs and a heavy malleable round headed retractor with two small hooks at the end for retraction of the diaphragm

The location of the incisions is shown in Figure 83 The first is made in the axillary region over the third rib which is exposed and resected about 12 cm The thoracic cavity is entered through the rib bed The lung is retracted the sympathetic gangliated trunk is located and the pleura overlying its upper five segments is divided The connections of the upper thoracic chain and stellate ganglions are severed The incision in the pleura is then extended over the sympathetic chain to the level of the eighth thoracic ganglions exposing the beginning of the planchnic nerve The roots of the gangliated trunk are cut down to the eighth ganglion, the origin of the splanchnic nerve is freed and the chain is dropped down into the lower thoracic cavity The incision in the che t wall is closed

A second lateral incision is then made over the cour e of the tenth rib and 12 14 cm of its length ,. — The th

hypertension because of the inherent vascular reactivity of the patient or because of his glandular make up

Patients with grade 4 hypertension (malignant nephrosclerosis) are not benefited by any operative procedures Those with grades 2 and 3 hypertension are

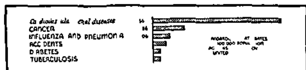


Fig 85—M t lity t t st t k n f m th d ta f th M t p lt n L f I u C mp y

greatly improved if complete splanchnic nerve section is *performed and patients with grade 1 (early or mild* hypertension) have been completely cured Caution is necessary to prevent confusing the early hypertension of young persons in grade 1 with arteriosclerotic hypertension of patients in the fifties The latter have a high pulse pressure and may have a high systolic pressure but their diastolic pressure is frequently around 100 mm Hg This latter condition is not considered here

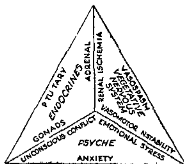


Fig 86—P th g f hype t (e d wn f m W) B f [} m d m d ı f t t ı l d h d t ry f t

The following procedures have been used supradiaphragmatic splanchnic nerve section infradiaphragmatic splanchnic nerve section transdiaphragmatic splanchnic nerve section omental or muscular graft into the kidney nephrectomy and renal biopsies Thirty patients had adequate follow up study There were 4 with supradiaphragmatic 15 with infradiaphragmatic and ı with transdiaphragmatic

fication preoperative study indications and technic of surgery and early and late results in cases of hypertension The pathologic conditions in 44 patients are given in Table 1 A modification of Schroeder and Steele's classification has been used for a working basis (Table 2) In an attempt to assign to these various factors a proper relationship Edward Weiss constructed a diagram to illustrate them (Fig 86) This shows that the presence in a person of one factor such as renal ischemia following eclampsia with a noncontributary family history and no constitutional factors may not lead to hypertension whereas in another person a small emotional environmental or toxic stress may bring on

TABLE 1 —CONDITIONS IN SURGICALLY TREATED PATIENTS WITH HYPERTENSION (JUNE 1 1940)

DIAGNOSIS	NO OF PATIENTS
Atrophic pyelonephritis	2
Lupus kidney	1
Congenital hypoplastic kidney	3
Eclamptic kidney	3
Adrenal medullary tumor	2
Benign nephrosclerosis	25
Malignant nephrosclerosis	8
Total	44

TABLE 2 —CLASSIFICATION OF CLINICAL LESIONS IN ARTERIAL HYPERTENSION

RENAL		NERVOUS	ENDOCRINE
A Parenchymal	B Vascular		
Glomerulonephritis	Arteriosclerosis	Brain tumor giving rise to increased intracranial pressure	Pituitary basophilism
Pyelonephritis	Buerger's disease		
Urinary obstruction	Periarteritis nodosa	Disease of the brain stem (bulbar poliomyelitis)	Adrenal tumor (of medulla and cortex)
Renal tumor	Renal infarct		Hyperthyroidism
Amyloid kidney	Lupus erythematosus	Psychic disturbance	Ovarian tumor
Polycystic kidney	Lead poisoning		Menopause
Hypoplastic kidney	Coarctation of the aorta		Obesity
Eclamptic kidney			

Hypotension

Association of Postural Hypotension with Sympathetic Nervous System Dysfunction Case Report, with Review of Neurologic Features Associated with Postural Hypotension Richard H Young[7] (Omaha) states that the term orthostatic or postural hypotension has been applied to a condition characterized by a marked fall in the systolic and diastolic blood pressures when the patient changes from the recumbent to an erect posture The salient features besides the orthostatic hypotension in order of frequency are (1) weakness (2) anhidrosis or hypohidrosis (3) increased distress in summer (4) greater urinary frequency at night (5) variation in pulse rate with change in posture (6) loss of libido and potentia (7) orthostatic syncope with loss of consciousness (8) low basal metabolic rate —10 or lower (9) blood urea of 40 mg per 100 cc or more (10) pallor (11) secondary anemia (12) false appearance of youth and (13) neurologic signs

Ellis and Haynes reported six cases in four of which there was definite evidence of neurologic disease and an *additional case in which there was some evidence of* involvement of the central nervous system They believe that postural hypotension results from failure of the normal sympathetic vasomotor reflex to produce vasoconstriction when the subject assumes an erect position Because of the widespread effect they believe that the site of the lesion is either in a sympathetic center or in an efferent pathway controlling the entire response or is generalized throughout the efferent pathways and nerve endings

Young s case aroused interest in the neurologic features of the disorder Further stimulation was provided by the report of Ransom Kabat and Magoun on the autonomic responses to electrical stimulation of the hypothalamus preoptic region and septum In certain indefinite regions it was possible by electrical stimulation to obtain a marked fall in blood pressure and changes in

(7)—Ann Int Med 15 910 916 November 1941

splanchnic nerve section Five had omental or muscular graft and one nephrectomy for hypertension There was no surgical mortality Supradiaphragmatic and infra diaphragmatic splanchnic nerve sections yielded such doubtful results that they were discontinued Transdia phragmatic total splanchnic nerve section has given ex cellent results but it failed in one patient with malignant nephrosclerosis Of five patients with grade 4 hyperten sion in whom a renal graft was made only one, now fol lowed for five years has had subjective relief One pa tient who had nephrectomy for unilateral atrophic pyelonephritis and one who had nephrectomy for con genital hypoplastic kidney had complete subjective and objective relief The different mechanisms which may bring about relief in hypertensive patients after splanch nic nerve section are listed in Table 3

TABLE 3 —MECHANISM OF RELIEF IN HYPERTENSIVE PATIENTS AFTER EXTENSIVE SPLANCHNIC NERVE SECTION

Actual lowering of blood pressure (diminution in size of heart and improvement in electrocardiogram)
Pronounced polyuria diminished excretion of protein and improvement in renal function (immediate or gradual)
Postural hypotension with consecutive decrease in venous pressure and effective circulating blood volume decrease in papilledema and improvement in cerebral circulation
Decrease in reflex nervous irritability due to adrenal denervation
Diminished sensitivity to epinephrine increased sensitivity to insulin
Disappearance of palpitation of heart and dizziness even if basal blood pressure in horizontal position is unchanged

The authors conclude that surgical therapy so far is *the most effective method of checking the progress of* hypertension The selection of patients with early hyper tension and the use of improved technic seem to be two important factors in obtaining good results Aside from actual lowering of blood pressure the gradual improve ment of renal function postural hypotension and de crease in reflex nervous irritability due to adrenal denervation constitute the mechanisms of the relief obtained

HYPOTENSION

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bladder contractility Young's case showed the clinical features of a bradykinetic type of parkinsonian syndrome associated with marked postural hypotension and other manifestations of sympathetic nervous system dysfunction As a result of the pharmacologic experience in this case it is suggested that the best method of therapy is one which produces sympathetic stimulation with ephedrine or benzedrine and parasympathetic inhibition by drugs of the atropine group

Psychoneurosis

Cardiac Neurosis and Heart Disease F A Willius[8] emphasizes the importance of recognition on part of the physician of the possibility of coexistence of structural heart disease and cardiac neurosis Such a structural impairment of an organ may be complicated by a superimposed neurosis and under such circumstances any and all symptoms should not be attributed to the existent disease Failure on the part of the physician clearly to separate the genuine from the spurious manifestations frequently leads to long periods of useless and unnecessary invalidism

Rheumatic Fever

Study of 70 Rheumatic Families Arthur Rosenblum and Ruth L Rosenblum[9] (Chicago) report their conclusions from study of 70 low income families each with a rheumatic child attending the public schools

There was marked incidence of rheumatism in other family members The families with rheumatic parents had a higher incidence of the disease among the siblings than those with nonrheumatic parents Incidence was higher after association with a person with active rheumatism this was higher in families with rheumatic parents than in families with nonrheumatic parents. Simultaneous attacks of rheumatism were frequently noted among siblings and among parents and siblings

(8) Proc Staff Meet Mayo Clin 16 575 576 Sept 3 1941
(9) Am Heart J 3 73 83 January 194

Waves of respiratory infections prior to those attacks were not noted

Respiratory infections occurred preceding onset of the first manifestations of rheumatism in slightly less than one half of the cases Scarlet fever preceded onset in 10 per cent In the cases not preceded by respiratory infections such factors as exposure to dampness chilling tonsillectomy and psychic trauma were present In a number of cases there was no illness preceding onset of first rheumatic symptoms Tonsillectomy did not seem to influence rheumatic recurrences The older the child at time of tonsillectomy the fewer the recurrences Generally however the patients with severe heart damage had not had tonsillectomy or had had it after onset of rheumatism

FAMILY INCIDENCE AS INFLUENCED BY DIFFERENT CRITERIA FOR DIAGNOSIS

	Definite Rheumatic Cases		Including Questionable Cases	
	N	%	N	%
Families with other rheumatic members	35	50	45	64
Families with other rheumatic siblings	13	18 6	29	41 4
No of other rheumatic siblings	20	6 2	51	15 9
Families with rheumatic parents	19	[illegible] 2	0	4[illegible] 8
No of rheumatic parents	20	14 3	3	[illegible]3 6
Families with rheumatic grandparents	4	6 5	6	8 6
No of rheumatic grandparents	4	1 4	6	2 [illegible]5

Analysis of the incidence of rheumatism as compared with family income showed a higher incidence in the self supporting group than in the relief group The self supporting group was on a marginal income level however There appeared to be no correlation between number and severity of attacks and none between incidence of rheumatism and presence of vermin Dampness was the only home condition factor that could be correlated with increased incidence of rheumatism but there was no correlation between dampness and number and severity of attacks No relation between diet and

occurrence of rheumatism could be found most of the families in this study did not have an optimum diet

The outstanding observations were the marked familial trend in rheumatic fever and the tendency toward simultaneous flare ups in several members of the family If these are correct particular attention should be paid to infection in other family members to prevent rheumatic infection in susceptible persons and to institute early treatment once infection has occurred

Rheumatic Heart Disease in Children Stanley Gibson[1] (Northwestern Univ) points out that any disease with a 10 per cent mortality rate is serious Predisposing causes include damp and cold climate, poor economic status and respiratory infections The first manifestation of rheumatic fever is pain in various joints the child should not go home from the hospital as soon as the pains have subsided because careful laboratory and clinical examinations are required to determine the health of the child He should usually be kept in bed for a month once diagnosis of rheumatic fever has been definitely established to await return of a normal sedimentation rate Chorea is the second manifestation of rheumatic fever Every child who has chorea should be *looked on as a potential sufferer of rheumatic heart disease* Of 600 patients with chorea 2 out of 5 eventually developed organic heart damage The third manifestation is involvement of the heart itself

The problem of the cardiac cripple the children who become adult patients with mitral stenosis usually at 25, 35 or 40 is a serious one White states that about 35 per cent of all cases of heart disease in Boston are due to rheumatic fever and Lewis in London gives almost the same figures for the incidence of rheumatic heart disease To prevent rheumatic heart disease a good deal can be done by early recognition of the significance of joint pains and chorea Proper treatment at this time is imperative Removal of the child to a sunny climate is helpful Prophylactic administration of sul

fanilamide to prevent streptococcic infection of the throat which usually precedes rheumatic invasion appears to be encouraging Experiments indicate that use of sulfanilamide in relatively small doses through the rheumatic fever season beginning about October and continuing until June may prevent recurrence even in climate such as that of New York City and Baltimore

[From a physician standpoint it would be comforting to think that tonsillectomy administration of sulfanilamide through the rheumatic fever season a high vitamin C diet immunization against rheumatic fever removal to a sunny climate or treatment in a convalescent heart hospital really help to prevent rheumatic heart disease or l en the pathologic damage to the heart but we have no definite proof that any of these measures are positively beneficial.—Ed]

Cardiac Signs in Rheumatic Infection of Childhood Rachel Ash[3] (Univ of Pennsylvania) describes the cardiac signs for 553 children with rheumatic infection observed for 9 6 years since onset of infection Severity of the disease was greatest in children first taken ill with acute carditis and the outcome was most favorable for those whose initial manifestation was chorea Death rate was higher during the first year after onset than any single year thereafter Percentage incidence of deaths was greater among boys than girls and higher among the Negro than the white children Diagnosis of valvular heart disease was made in 64 per cent of the group 61 per cent were leading a normal existence Five per cent were either cardiac invalids or had recurrences of rheumatic infection Twenty four per cent had died of heart disease A comparison of these results with those of other observers is outlined in Table 1

The condition of 19 per cent of the group without cardiac enlargement or murmurs during the initial illness was classified as potential heart disease In an additional 19 per cent the heart had remained within normal limits in size but systolic murmurs usually considered accidental or functional were audible these were classified as having potential and possible heart disease The appearance of some degree of cardiac enlargement with

(3) Am J D Child 63 1 14 J ry 194

TABLE 1 —OUTCOME IN CASES OF RHEUMATIC INFECTION IN CHILDHOOD

Author	No of Patients Traced	Average Age at Onset Yr	Duration Yr	Incidence of Valvular Heart Disease %	Percentage of Patients: Dead	Percentage of Patients: Leading Normal Existence
Findlay (1931)	669	±7	2-22	78 9	23 1	
	561	±7	2-12	67 4	19 6	
Schlesinger (1938)	1 000	±7	1-10	73 8	12 3	81 7
Jones T D (1939)	1 000	8 0	Over 10	66 0	24 0	59 7
Wilson M G (1940)	717	6± 1	Av 8	99 5	16 3	66 6
Ash (present series) (1941)	553	6 9	3 17 Av 9 6	64 2	21 0	61 1

Card n f ment wa d g ed n t nly n accordan w th th te used f r the p sent tudy but in th pres nce f card c
l g m t l d t m n d by r tge e m n t on in f st l and obl qu i ws M n mal d ac damage wa present n ne th d f th a e

TABLE 2 —OUTCOME IN CASES OF ACUTE RHEUMATIC PERICARDITIS

Author	No of Patients Traced	Average Age at Onset of Acute Pericarditis Yr	Average Time Elapsed Between Pericarditis and Recovery or Death Yr	Immediate Mortality %	Total Mortality %	Complete Recovery %
Holt	43	Childhood	½-4		48 8	0 0
Findlay	61	8 5	1-17	47 8	63 4	2 1
Schlesinger	62	Childhood	6	33 3	50 0	11 0
Massie and Levine	104	19 6	7	16 3	40 2	28 8
Ash (present series)	81	8 3	9 7	10 0	75 0	2 5

N ld l h t d n phy l m t n

a systolic blow maximum at the apex with or without associated mid diastolic blow was accepted as indication of mitral disease A diastolic blow to the left of the sternum was interpreted as the result of involvement of the aortic valve Diagnosis of valvular disease was made for 62 per cent after recovery from the first manifestation of rheumatic infection

Probably the most marked difference between children with enlarged hearts associated with murmurs suggesting valvular damage and those with absence of or minimal signs lies in the degree of myocardial involvement and resultant dilatation which is dependent on severity of infection and resistance of the patient The course of children with potential or possible heart disease was more favorable not only at onset but throughout the succeeding 10 years of infection Despite recurrences the death rate remained relatively low

Regression of cardiac signs occurred in about 10 per cent of 340 cases in which diagnosis of heart disease was made after recovery from the initial illness In six cases both mid diastolic and systolic blows disappeared In the rest only systolic murmurs had been present In about half the cases disappearance of the signs occurred within a year in the remainder it occurred over a period of years In 39 of 209 cases in which an initial diagnosis of potential or possible heart disease was made definite cardiac lesions subsequently developed Incidence ranged from 5 per cent at the end of 1 year to about 20 per cent at the end of 5 years and 25 per cent at the end of 10 years among patients who had recovered from an initial attack of polyarthritis without obvious cardiac damage In cases with simple chorea at onset valvular lesions had developed in 4 per cent at the end of 1 year in 21 per cent at the end of 5 years and in 31 per cent at the end of 10 years Subsequent signs of valvular deformity appeared in 32 of the cases in association with acute recrudescences of rheumatic fever In apparent absence of infection and after prolonged periods the murmur of mitral stenosis became

audible in five cases that of aortic insufficiency in one

The systolic screech was present in 48 cases in all but 2 of which it was associated with acute carditis which terminated fatally in 6 In five cases with marked rheumatic heart disease and persistent low grade infection the whistling murmur remained from two to nine years

Of 81 cases with a pericardial friction rub 75 per cent terminated fatally Of the survivors five were cardiac invalids The experience of others confirms the poor prognosis after acute pericardial involvement (Table 2)

Aortic disease as a cardiac sign was second in order of severity to acute pericarditis Aortic insufficiency developed in 110 cases 59 of which were fatal A transitory diastolic blow to the left of the sternum was audible in an additional 10 cases of acute carditis Chorea was rare as an initial sign Aortic involvement appeared during the initial illness in 41 cases proving fatal in 12 Death occurred subsequently in 15 As a terminal manifestation aortic insufficiency was present in 18 including the 12 in which death occurred during the first attack In six an aortic diastolic murmur made an insidious appearance during low grade activity of the infection Inconstance at onset was noted in 18 the murmur appearing and disappearing but eventually becoming constant In 11 cases the patient recovered from one or more attacks of rheumatic illness with an apparently normal heart only to have persistent signs of aortic and mitral damage develop as a result of acute recrudescence In one boy aortic insufficiency had appeared insidiously in the seeming absence of infection Except for this case there was some evidence of mitral disease in all cases in which the aortic valve became involved In 57 cases a mitral lesion preceded the appearance of aortic disease

Further Studies in Immunization against Rheumatic Fever Twice before Valentina P Wasson and Edward E Brown[4] (New York Post Graduate [illegible] have re-

[4] [illegible] Am Heart J 3 [illegible] March 19[illegible]

corded satisfactory results of immunization of ambulatory patients with rheumatic heart disease Sixty six carefully controlled patients received graduated injections of hemolytic streptococcus filtrate prior to 1939 The authors report here the condition of 35 more rheumatic cardiac children who received a two year course of treatment since then After eight years of trial of this method the authors state that the treated patients have shown a striking reduction in the number of attacks of acute rheumatic fever and a marked general

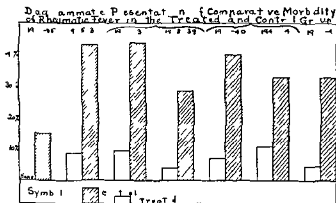


Fig 87

improvement in health Many formerly treated patients have been observed for as long as six years since injections were discontinued and their health has remained materially better than that of untreated patients If a hemolytic streptococcus toxin has been able to confer immunity on them that immunity is of long duration Bacteriologic studies show that treated patients would get upper respiratory infections but they would be of short duration and seldom followed by a flare up

The authors tried an abbreviated method of immunization on 42 children giving them the total number of skin test doses in 4 instead of 38 inoculations intra

dermally *three weeks apart* The N Y 5 toxin has been attenuated with tannic acid and the intradermal route allows a slow absorption of the toxin Reactions have been only local but in a number of highly sensitized *children they were* as large as 5 7 *cm in diameter* The only subjective symptom was *itching* 24 hours later Some patients received preliminary skin tests for determining sensitivity Almost *every* patient in this group received the *first* semiannual inoculation in May or *June 1941* Only *prolonged observation* will show whether the results of *this form* of treatment are as lasting as those of the protracted treatment

Prophylactic Use of Sulfanilamide on Rheumatic Patients The *study on two groups of rheumatic* children reported by David Dudley Stowell and William H Button Jr[5] (Roosevelt Hosp New York City) showed that sulfanilamide *failed as* a prophylactic for *the* ambulatory *rheumatic patient* and *therefore should* not be used Simple reduction in dosage will diminish the toxicity nevertheless no large group of children can take the drug in any dosage over the necessary *8 to 10* winters without *some mortality* from its use In the authors group one death occurred which can be attributed to the drug

Syphilis

Early Diagnosis of Syphilitic Aortitis S Bohrens Lester Hollander and Maurice Goldsmith[6] (Montefiore Hosp New York City) *repeated previously emphasized* methods of examination to determine their value in diagnosis of early or uncomplicated syphilitic aortitis, 200 patients with syphilis and 200 normal *controls* were used

An analysis of the Vaquez Bordet measurement in 200 normal patients revealed a wide variation in the size of the normal aorta—3 9 7 8 cm No definite *relation* could be demonstrated between *size of* aorta and *race sex* height, weight chest diameter, occupation and age although there was *a tendency to* increase *in size of the*

(5) J A M A 117 1642166 Dec 0 1941
(6) Am J M Sc 203 4 63 January 194

aorta in obese or older patients It is impossible to determine a standard of normal measurement because of the marked variability of the normal aorta A summary and comparison of the Vaquez Bordet measurements of the 200 nonsyphilitic and 200 syphilitic patients by age groups is shown in the table The impressive feature of this comparison is that with a few exceptions the two



Fig 88—P t t d l ft bl q t le ntg gr m sh wi g
d ff d l t f t

groups present identical measurements The increase of size of the aorta is almost the same with advancing years in syphilitic and nonsyphilitic patients and is apparently due to arteriosclerosis

Physical examinations and electrocardiograms as well as the roentgen examinations revealed that there is no single pathognomonic sign of early syphilitic aortitis discernible by these methods In 1932 Moore Danglade and Reisinger established diagnostic criteria for uncomplicated syphilitic aortitis These were (1) teleroentgenographic and fluoroscopic evidence of aortic dilatation (2) increased retromanubrial dulness (3) history of circulatory embarrassment (4) a tympanic bell like accentuation of the aortic second sound (5) progressive cardiac failure (6) substernal pain and (7) paroxysmal dyspnea The authors are convinced that these criteria are not diagnostic of uncomplicated syphilitic aortitis but are characteristic of aortitis with serious complica

dermally three weeks apart The N Y 5 toxin has been attenuated with tannic acid and the intradermal route allows a slow absorption of the toxin Reactions have been only local but in a number of highly sensitized children they were as large as 5 7 cm in diameter The only subjective symptom was itching 24 hours later Some patients received preliminary skin tests for determining sensitivity Almost every patient in this group received the first semiannual inoculation in May or June 1941 Only prolonged observation will show whether the results of this form of treatment are as lasting as those of the protracted treatment

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(5) J A M A 117 164 2166 Dec 0 1941
(6) Am J M Sc 03 4 6 J u ry 1942

per cent (91 of 2718) One half of these patients with aortic regurgitation denied any symptoms of cardiac insufficiency at diagnosis Only 31 of the 91 patients sought medical care because of symptoms referable to the heart 53 sought care for noncardiac complaints and 7 were seen after routine serologic testing of supposedly well people Of 28 of the asymptomatic patients followed over two years 2 have died of heart disease and only 2 have developed symptoms Circulatory studies including vital capacity venous pressure circulation time and roentgenoscopy of 47 of these patients showed a close correlation with the clinical impression of their cardiac status Aortic width was normal in 37 of 87 of the patients with aortic insufficiency In only 3 of 135 patients with syphilitic aortic insufficiency was the blood Wassermann reaction negative in the absence of a history of previous antisyphilitic treatment (Table 2)

TABLE 1 —Period of Observation of 91 Patients with Syphilitic Aortic Insufficiency

Years	Number of Patients		
	Group I	Group II	Group III
Less than 1	14	2	11 (5 deaths)
1–	11	3	7 (1 death)
2– 3	8	2	8 (1 death)
3– 4	5	5	1
4– 5	2	1	3 (1 death)
5– 6	0		1
6– [illegible]	1		–
7– 8	2		
8– 9	0		
9 10	2		
	43 (4 deaths)	13 (1 death)	33 (8 deaths)

[illegible]

The authors conclude that aortic insufficiency due to syphilis is present in a clinically recognizable form for a ratl [illegible] g time before development of symptoms

tions Apparently Moore and his co-workers used the term uncomplicated aortitis inconclusively By uncomplicated aortitis they understood a "supravalvular involvement of the aortic wall with or without diffuse dilatation but without valvular insufficiency or saccular aneurysm" They failed to consider the condition of the coronary vessels at autopsy in subjects with cardiac symptoms This is particularly important, since a well recognized cause of cardiac failure is syphilitic involvement of the coronary orifice Stenosis or occlusion of the coronary orifice has been found at autopsy in 10 to 35 per cent of cases of syphilitic aortitis Careful pathologic studies have shown that (1) uncomplicated syphilitic aortitis is symptomless and (2) that cardiac symptoms in a syphilitic patient are due to complications of aortitis i e saccular aneurysm valvular insufficiency or stenosis of the coronary orifice or some unrelated condition such as degenerative or rheumatic heart disease

Roentgen examination is a valuable aid in the diagnosis of late aortitis at times being the first or only indication that such a condition exists

COMPARISON OF THE VAQUEZ BORDET MEASUREMENT IN NORMAL AND SYPHILITIC SUBJECTS

AGE	EXTREME VARIATIONS OF AORTIC WIDTH (CM)	AVERAGE AORTIC WIDTH (CM)
20-30	3 9-6 6	5 0
20-30	*3 2-6 7*	*5 0*
31-40	4 8-7 6	5 8
31-40	*4 6-7 5*	*5 8*
41-50	4 7-7 4	6 2
41-50	*4 8-10 0*	*6 7*

Bl ck no m l ital yph litic

Syphilitic Aortic Insufficiency The Asymptomatic Phase Walsh McDermott (Cornell Univ), Ralph R Tompsett (New York Hosp) and Bruce Webster[7] (Cornell Univ) report that in a 4½ year period in the syphilis division of New York Hospital incidence of syphilitic aortic insufficiency without aneurysm was 3 3

(7) Am J M Sc 03 0 15 Febru ry 1942

per cent (91 of 2,718) One half of these patients with aortic regurgitation denied any symptoms of cardiac insufficiency at diagnosis Only 31 of the 91 patients sought medical care because of symptoms referable to the heart 53 sought care for noncardiac complaints and 7 were seen after routine serologic testing of supposedly well people Of 28 of the asymptomatic patients fol lowed over two years 2 have died of heart disease and only 2 have developed symptoms Circulatory studies including vital capacity venous pressure circulation time and roentgenoscopy of 47 of these patients showed a close correlation with the clinical impression of their cardiac status Aortic width was normal in 37 of 87 of the patients with aortic insufficiency In only 3 of 135 patients with syphilitic aortic insufficiency was the blood Wassermann reaction negative in the absence of a history of previous antisyphilitic treatment (Table 2)

TABLE 1 —PERIOD OF OBSERVATION OF 91 PATIENTS WITH SYPHILITIC AORTIC INSUFFICIENCY

	Numb[illegible] Pa[illegible]		
[illegible]	G[illegible]p I	G[illegible]p II	G[illegible]p III
Less than 1	14	2	11 (5 deaths)
1–2	11	3	7 (1 death)
[illegible] 3	8	2	8 (1 death)
3–4	5	5	1
4–5	2	1	3 (1 death)
5–6	0		1
6–7	1		
7–8	2		
8–9	0		
9–10	2		
	45 (4 deaths)	13 (1 death)	33 (8 deaths)

[illegible]

The authors conclude that aortic insufficiency due to syphilis is present in a clinically recognizable form for a rather long time before development of symptoms

tions Apparently Moore and his co workers used the term uncomplicated aortitis inconclusively By uncomplicated aortitis they understood a "supravalvular involvement of the aortic wall with or without diffuse dilatation but without valvular insufficiency or saccular aneurysm *They failed to consider the condition of the* coronary vessels at autopsy in subjects with cardiac symptoms This is particularly important since a well recognized cause of cardiac failure is syphilitic involvement of the coronary orifice Stenosis or occlusion of the coronary orifice has been found at autopsy in 10 to 35 per cent of cases of syphilitic aortitis Careful pathologic studies have shown that (1) uncomplicated syphilitic aortitis is symptomless and (2) that cardiac symptoms in a syphilitic patient are due to complications of aortitis i e saccular aneurysm valvular insufficiency *or stenosis of the coronary orifice or some unrelated* condition such as degenerative or rheumatic heart disease

Roentgen examination is a valuable aid in the diagnosis of late aortitis at times being the first or only *indication that such a condition exists*

COMPARISON OF THE VAQUEZ BORDET MEASUREMENT IN NORMAL AND SYPHILITIC SUBJECTS

AGE	EXTREME VARIATI N OF AORTIC WIDTH (CM)	AVERAGE A TIC WIDTH (CM)
20-30	3 9-6 6	5 0
20-30	*3 2-6 7*	*5 0*
31-40	4 8-7 6	5 8
31-40	*4 6-7 5*	*5 8*
41-50	4 7-7 4	6 2
41 50	*4 8-10 0*	*6 7*

Black normal *ital c syphilit*

Syphilitic Aortic Insufficiency **The Asymptomatic Phase** Walsh McDermott (Cornell Univ) Ralph R Tompsett (New York Hosp) and Bruce Webster[7] (Cornell Univ) report that in a 4½ year period in the syphilis division of New York Hospital incidence of syphilitic aortic insufficiency without aneurysm was 3)

(7) Am J M Sc 203 0 15 F b uary 194

ment directed toward syphilis has been energetic in earlier years may often be singled out as the ones in which no treatment is needed Intensive treatment such as is given in early syphilis is seldom indicated in late cardiovascular sequelas Although beneficial results may be noted with conservative arsphenamine therapy the heavy metals generally speaking are considered safer and produce equally satisfactory therapeutic results

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ANATOMIC DIAGNOSIS

Thrombosis of Coronary Arteries

Some Immediate Causes of Cardiac Infarction Ernst P Boas[1] (New York City) discusses the question whether cardiac infarction is a fortuitous occurrence or whether there are specific recognizable preceding circumstances Lately so called premonitory symptoms of cardiac infarction have been recognized and it is known that changes in the coronary circulation which eventually lead to complete arterial occlusion may develop over days or possibly weeks Lack of differentiation between attacks of angina pectoris coronary occlusion and coronary insufficiency has been confusing Angina pectoris indicates the particular type of heart pain usually induced by exertion or excitement of short duration and not followed by permanent myocardial damage Yet it is now accepted that every attack of angina pectoris is due to transient coronary insufficiency and that an electrocardiogram taken during pain may show changes indicating heart muscle damage these changes disappear promptly after the attack The concept of coronary occlusion is usually associated with dramatic and severe symptoms such as shock fall in blood pressure fever and heart failure with progressive electrocardiographic changes Actually it is often difficult to ascertain whether an attack of heart pain represents simple angina or coronary occlusion

(1) [illegible] t J 3 1 15 J [illegible] 194

This form is encountered in about one half of the patients with valvular syphilis Present day prognostic data based as they are on the course following onset of symptoms of failure are not applicable to this large group with cardiovascular syphilis

TABLE 2 —INCIDENCE OF POSITIVE WASSERMANN REACTIONS IN 135 PATIENTS WITH SYPHILITIC AORTIC REGURGITATION

	No of Patients	%
Positive blood Wassermanns	110	81 5
Doubtful (1–3+) blood Wassermanns but history of previous positive Wassermann and therapy	14	10 4
Negative blood but positive spinal fluid Wassermann	2	1 5
Doubtful (1–3+) blood Wassermann with no history of previous positive or therapy	6	4 4
Negative Wassermann no history of previous positive Wassermann or of therapy	3	2 2

Principles of Treatment of Cardiovascular Syphilis U J Wile[8] (Univ of Michigan) states that the fundamental principles governing treatment of cardiovascular syphilis embrace careful appraisal of each case with regard to therapeutic response which might reasonably be expected from the type of lesion present The most favorable cases from the standpoint of therapeutic response following antisyphilitic treatment are those in which cardiovascular disease exists with signs but no symptoms and in which inadequate or no treatment has been given Dysfunction and failure in these cases seem definitely postponed The benefit derived in such cases from a nonintensive but continuous form of treatment must be due partly to absorption of syphilitic residua in other parts of the body than in the circulatory stem as well as from the effects of treatment on syphilitic residua in the appreciably affected organs The presence and persistence of syphilitic foci remote from the heart must be recognized as a contributory factor in the ultimate failure in untreated cases

The treatment in cases in which failure is present should be no different from that given for heart failure from other causes Asymptomatic cases in which treat

(8) Ann Int M d 15 817 8 0 N mb r

if a man year in and year out carries on a laborious occupation and during this usual occupation sustains a cardiac infarction, the cardiac accident may have been caused by the stress of his work but it is not compensable But if some exceptional circumstance immediately precedes the cardiac symptoms i e if he has to lift some unusually heavy weight or if he slips while lifting the unusual strain will be regarded as cause of the cardiac disability and therefore compensable This law is active in many states Cardiac symptoms should accompany or immediately follow the event to which the cardiac injury is ascribed If symptoms are immediately disabling the causal connection is clear If a lapse of days occurs between accident and complete disablement there must be continuity of symptoms dating from the event

[I cannot agree with Boas that physical effort and emotion frequently contribute to development of a myocardial infarct I think it is much more often coincidental —Ed]

Coronary Occlusion in the Young Adult B E Konwaler and Thad Sears (Pueblo Colo) report a case in which the youth of the patient was of particular interest Despite his 29 years he presented far advanced coronary atherosclerosis which involved contrary to rule the right coronary far more than the left No family predisposition could be elicited Actually the family history of three generations appeared particularly free of vascular disease One of the puzzling features was the ease with which the patient repeatedly discharged emboli to both the pulmonary and the systemic circulation *This was clarified by the later findings* of large mural thrombi in both right and left ventricles

Man 29 married was the third in a family of five children Shortly after taking food and while walking he was seized with agonizing pain under the lower third of the sternum and severe pain over the axillary surfaces of both arms and below the elbows with numbness of the hypothenar eminences of both hands Past history disclosed two attacks of ptomaine poisoning and several brief attacks of indigestion consisting of epigastric pain following exertion and lasting two or three

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Boas reports cases which illustrate the fact that onset of cardiac infarction often is preceded by specific events apparently directly responsible. In one case, anginal symptoms appeared during severe effort while pushing a stalled car followed 12 hours later and again five days later by prolonged spontaneous attacks of anginal pain. After the second spontaneous attack classic angina of effort set in and continued. Throughout this period while cardiac infarction occurred, the patient continued to work. The electrocardiogram showed low voltage and abnormal RT segments in leads I, II and IV.

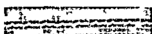
Present knowledge of physiology and pathology of the coronary circulation suggests the probable mechanism that may initiate cardiac infarction. Fundamentally there is upset of balance between nutritive needs of the heart muscle and the adequacy of the coronary blood flow sufficient to cause myocardial necrosis. Such coronary insufficiency arises usually because the narrowed channels of the diseased coronary arteries do not permit passage of enough blood to satisfy the needs of the heart muscle when there are sudden calls on it for greater work, blood flow is decreased because of reflex narrowing of the damaged coronary arterial bed or by hemorrhage into the coronary arterial wall causing partial or complete occlusion of one of the coronary vessels. The commonest external factors which precipitate cardiac infarction are effort, emotion, cold and overeating but they cannot cause cardiac infarction in presence of normal coronary arteries. Boas saw several patients in whom an intercurrent infection appeared to precipitate coronary thrombosis or cardiac infarction. In one patient with peptic ulcer for 13 years, anginal pains developed after a cold or mild grip; seven weeks after onset the electrocardiogram showed left axis deviation and a diphasic T wave in lead IV.

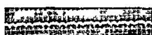
The question of compensation to workmen for disability is of interest in this field. Recognition of the fact

by emboli but in one leg the embolus apparently formed a ball valve since circulation could be restored in the foot by massage over the popliteal space In the fourth month two violent abdominal episodes occurred There were nausea vomiting unbearable umbilical pain and pain in the renal angles He went into shock and white cell count rose to 22 000 Autopsy revealed that the latter findings were the result of occlusion of both main renal arteries

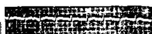
Repeated blood cultures were negative Serious anemia was never present *Urine showed no significant findings and other*









Fg 91 (l ft) —El t d g m m d l h ft tt k N t h gh t k ff f RT gm t n l d II l ft xi d t d h rp T n l ds I III d IV

Fg 9 (ght) —S d ft t n f T w n l d II

tests on the blood were negative Electrocardiographic studies several hours after the attack showed a definite high take off of the RT segment in lead I and left axis deviation with sharp T waves in leads I III and IV Another electrocardiogram made later showed inversion of T waves in lead II but otherwise marked improvement

At autopsy dry gangrene of the right big toe was found The brain showed numerous small emboli hemorrhages and marked cerebral edema The lungs showed numerous bilateral infarcts one of which had undergone necrosis with formation of an abscess cavity The vessels leading to the infarcted areas were thrombosed The main renal arteries were occluded and extensive renal infarction was present Numerous infarcts were present in the spleen and thrombi were present

minutes Exertional dyspnea was denied The only significant past illness was influenza a few months before the present illness and from which recovery was difficult

Physical examination showed the face of ashen color, reflecting anxiety There were cold sweat over the body and great exhaustion Pulse was 100 thready and irregular Blood pressure was 100/90 Respirations were fast and shallow Auscultation over the chest revealed no diagnostic findings in either heart or lungs A few hours after onset temperature was 101 F and white cell count 12,000 Blood



Fig 89 (left) —Film taken two months before present illness No significant heart or lung findings
Fig 90 (right) —Th[illegible] after onset, film shows [illegible] of cardiac enlargement

pressure dropped to 82/72 The patient was nauseated and complained of a tight bandlike constriction around the chest

He was given morphine and placed in an oxygen tent Substernal pain recurred for many days and two weeks after the first attack a second attack of equal severity occurred Three weeks after onset there was rapid dilatation of the heart. This was controlled by 27 cat units of leaf digitalis given in 3 unit doses at four hour intervals During the course he experienced four recurrent attacks of saphenous phlebitis He repeatedly expectorated small amounts of bright blood at the same time temperature would rise and physical findings of pulmonary embolism would appear At one time, evidence of extensive pericarditis appeared The seventh week of illness there was marked atrophy of the right arm and leg with motor and sensory loss and evidence of embolism to the internal capsule Later, there occurred paralysis of the left arm and leg In the third month both popliteal arteries were occluded

layer where a deposit of cholesterol ester occurs This may cause a proliferative reaction with formation of a nodule projecting into the lumen The lesions characteristically will be irregularly distributed so that the lumen is not symmetrically narrowed Later liquefaction necrosis with ulceration may occur and still later lime salts will be deposited in the fatty material leading to calcification In the aorta this process will not sufficiently affect the size of the lumen However in vessels like the coronary arteries or cerebral vessels it may cause marked narrowing of the lumen As a result of irregular obstruction of the lumen numerous whirlpools and eddies are formed leading to eventual thrombosis in a large percentage of cases The case reported here adds further proof that coronary occlusion can occur in the young adult without apparent hereditary basis for the atherosclerosis as suggested by others

Factors Influencing Immediate Mortality after Acute Coronary Occlusion Robert M Woods and Arlie R Barnes[3] (Mayo Clinic) studied records of 128 patients with acute coronary occlusion to ascertain the factors which caused death of 60 within six weeks while the remaining 68 survived the immediate period (Fig 94) Average age of all was 55 average age of those who survived was 51 3 as compared with an average age of 59 2 for those who died Incidence of immediate mortality among those with acute coronary occlusion after 60 was about twice as high as that among those with acute coronary occlusion before 60

Males predominated in a ratio of 5 4 1 but incidence of immediate mortality among males was only 41 7 per cent as compared with an incidence of immediate mortality of 75 per cent among women probably due to the fact that most men have acute coronary occlusion before 60 whereas most women with acute coronary occlusion have it after 60 Incidence of immediate mortality among patients with anterior apical infarcts and those who had posterior basal infarcts was exactly

in both popliteals The pericardial sac was obliterated by adhesive pericarditis, which could be separated by hand and appeared fairly recent The heart was *not* significantly en larged The right coronary artery showed extensive athero sclerosis of the main branch Microscopically, the right coro nary showed almost complete obliteration of the lumen with only small canalization All stages of atherosclerosis could be studied in various regions of the right coronary The left *coronary* howed moderately *advanced* atherosclerosis in the interventricular branch with reduction in size of the lumen to about one half *normal* There was a recent antemortem mural thrombus at tached to the anter ior wall of the left ventricle and an *older* much more firmly attached thrombus to the pos terior wall of the right ventricle Mi *croscopic* sections of the right ventricle showed the firmly at *tached mural* throm bus and extensive infarction both re cent and old



F g 93 —Right co nary artery A athe oma t u plaque C nal t on Note mpl te *bl t at n f lumen except for nal z on*

Arteriosclerosis means in general hardening of the arteries This general grouping can be broken down into three types based on the portion of the wall and the size of the vessel involved (1) There is atherosclerosis involving primarily the subintimal layer of such vessels as the cerebrals the coronaries and the aorta (2) There is the common hardening of the periph eral vessels such as the radial and temporal arteries (3) There is the diffuse sclerosis seen in the small arterioles in essential hypertension Coronary atherosclerosis as in the present case is apparently secondary to a *disturbed cholesterol or fatty metabolism* If this tendency is inherited the process may occur in the young The pathologic change occurs first in *the subendothelial*

TABLE 2—SIGNIFICANCE OF DYSPNEA IN 208 PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

D ree Dys nea	P ie ts	Deaths	Mo tality
Absent	61	11	18
Mild	ɔ0	12	24
Moderate	58	21	36
Severe	ɔ9	?4	6?

Dyspnea of some degree occurred in 71 per cent Mortality increased decidedly as dyspnea became more prominent Dyspnea was much more helpful than pain in judging prognosis Sweating occurred commonly but had *only slight* prognostic significance Cyanosis was found in about half the patients and indicated a distinctly higher mortality Some degree of shock was present in 54 per cent of all patients Mortality increased in direct proportion to the degree of shock absent 20 per cent mild 26 per cent moderate 51 per cent and severe *93* per cent

TABLE 3—SIGNIFICANCE OF HIGHEST RECTAL TEMPERATURE IN 19ɔ PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

T mper ure (F)	P tienis	D aths	M ali
Up to 99 9	10	4†	40
100 to 100 9	68	14	21
101 to 101 9	54	18	33
102 to 10? 9	ɔ0	18	36
103 to 103 9	11	7	64
104 and over	6	5	83

P t ts whos t mpe t f ll this w l d d if th y w t bse d durı g th first w k f dis as

† Th f th f ur d th w f p t t wh te d th h p t l in hock d d d w thı f w h rs f th nit al ympt m f th tt k

Gallop rhythm was noted in 20 per cent of all patients and was more common among those who died It was more commonly associated with anterior than with posterior infarction but was a more serious sign for patients with the latter lesion The quality of heart sounds was regarded as faint in over half the patients and such sounds were more common in those who died Incidence of pericardial friction rub was 16 per cent Although generally associated with anterior infarction it was observed in five patients with a posterior lesion Its

Immediate mortality in the entire series was 33 per cent Anterior infarctions occurred more commonly than posterior lesions the proportion being 5 3 but mortality was about the same in both Mortality was distinctly higher for patients with bundle branch block and those with auriculoventricular block but lower for those who showed low voltage of the QRS complex A group that had electrocardiographic findings regarded unclassifiable, i e without significant changes or abnormalities also had distinctly lower mortality Proportion of men to women was 7 3 prognosis for women was somewhat more grave Average age at time of attack was 58 7 years for all 57 4 for men and 61 5 for women Mortality progressively increased with advancing years regardless of electrocardiographic findings Antecedent angina pectoris was present in 72 per cent of all and was equal in occurrence in the two sexes Patients with a previous history of such a condition had a lower mortality (29 per cent) than those without it (38 per cent) Antecedent hypertension was present in 57 per cent of all 44 per cent of the men and 86 per cent of the women It tended to increase the mortality in both sexes Coronary occlusion in women without previous angina pectoris or hypertension was particularly rare Occurrence of a fall in systolic blood pressure of more than 20 mm increased mortality slightly although a systolic level that was maintained below 80 mm for many hours or days appeared to be serious The severity or radiation of the pain had little prognostic value nor did it aid in localization of infarction However in the small number of patients without pain in the chest mortality was decidedly higher than average Anterior infarction with pain radiation to the left arm had a lower mortality than similar infarction without this radiation Radiation of pain to the right arm as well as to the left was slightly more common in association with posterior infarction Occurrence of initial attacks of myocardial infarction without any pain or its equivalent symptoms was rare

TABLE 2—SIGNIFICANCE OF DYSPNEA IN 208 PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Degree of Dyspnea	Patients	Deaths	Mortality %
Absent	61	11	18
Mild	50	12	24
Moderate	58	21	6
Severe	39	24	62

Dyspnea of some degree occurred in 71 per cent Mortality increased decidedly as dyspnea became more prominent Dyspnea was much more helpful than pain in judging prognosis Sweating occurred commonly but had only slight prognostic significance Cyanosis was found in about half the patients and indicated a distinctly higher mortality Some degree of shock was present in 54 per cent of all patients Mortality increased in direct proportion to the degree of shock absent 20 per cent mild 26 per cent moderate 51 per cent and severe 93 per cent

TABLE 3—SIGNIFICANCE OF HIGHEST RECTAL TEMPERATURE IN 199 PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Temperature (F)	Patients	Deaths	Mortality %
Up to 99 9	10	4†	40
100 to 100 9	68	14	21
101 to 101 9	54	18	33
102 to 102 9	50	18	36
103 to 103 9	11	7	64
104 and over	6	5	83

* P t ts wh temp t f ll this w l d d if th y w t bs d d g th fi t w k f dis

† Th ee f thes f ur d th wer f p t t wh t d th h p tal hock d d d w thi f w h ur f th t l ympt ms f th tt k

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Rectal temperature (Table 3) was above 100 F in 92 per cent In seven cases it was between 99 and 100 F *and in three below 99 F* There was a distinctly progressive rise in mortality with increasing levels of fever When changes in pulse rate due to such arrhythmias as paroxysmal rapid heart action and heart block were excluded the heart rate in most patients was over 100 (average 107) In seven patients the rate never rose above 80 and in one it was under 70 A slight *tendency to increased mortality accompanied the more* rapid rates Respiratory rates in general followed the pulse rate and degree of dyspnea and were on the whole more rapid in patients who died than in those who recovered A leukocyte count over 10 000 during the first week following onset of attack was found in 86 per cent In 3 per cent the count was under 30,000 Mortality was 16 per cent for those with counts under 15 000 and 34 per cent for those with counts over that level Sedimentation rates did not seem to be of much prognostic value

About three fourths of the patients showed some objective evidence of congestive failure Mortality steadily increased with increasing degrees of pulmonary congestion absent 10 per cent slight, 30 per cent moderate 44 per cent and marked 68 per cent A palpable liver was found in 29 per cent This seems more common than was expected but probably reflects the greater gravity of conditions in patients coming to a public hospital Presence of a palpable liver increased mortality slightly Peripheral pitting edema occurred in 22 per cent and was definitely associated with increase in mortality Left heart failure occurred more commonly but was slightly less serious with anterior than with posterior lesions Combination of both right and left heart failure was equally common with anterior and with posterior infarction It appeared that presence of right heart failure was somewhat more serious in patients with an anterior lesion

mplications such as pulmonary infarction, pneu

monia psychosis cerebral vascular accident and peripheral arterial embolus obviously made the outlook more serious Some type of arrhythmia was observed in 38 per cent of patients and tended to increase mortality slightly Auricular fibrillation almost always transient occurred in 12 per cent of patients paroxysmal ventricular tachycardia in 3 per cent paroxysmal auricular flutter in 2 5 per cent and extrasystoles of some form in 25 per cent Partial or complete heart block was present in 3 5 per cent and was more commonly associated with posterior than with anterior lesions The degree of block tended to decrease or disappear if recovery ensued Apparently absence of any significant changes in electrocardiographic tracings indicated a distinctly more hopeful immediate outlook

The authors conclude that the immediate outlook in a case of acute coronary thrombosis is extremely difficult to predict There is practically no infallible criterion Weighing all the information available together with the general appearance of the patient will enable the physician to make a fair *estimate* as *to immediate prognosis*

TABLE 4 —SIGNIFICANCE OF DEGREE OF PULMONARY CONGESTION IN 206 PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

D E	P TI	DE H	Mo TALI %
Absent	58	6	10
Mild	62	25	30
Moderate	32	14	44
Severe	34	23	68

D t g di g th po t wer us d d d q t fo tw p ti ts

II Ultimate Prognosis—Rosenbaum and Levine[5] present follow up studies on 372 cases For 271 still living survival rate was 27 6 months Average survival rate of 101 patients known to have died was 41 1 months About *one fourth of the deaths occurred within one* year one half within two years and three fourths within five years Four patients died more than 10 years after the initial attack Survival period of patients with QRS complexes of low amplitude was 38 3 months and of

(5) A h I t M d 68 1 151 31 D mb 1941

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Patients who had antecedent angina pectoris had more subsequent angina pectoris more congestive failure and a lesser degree of recovery of activity but lived about as long as those without previous angina pectoris

In a group of 80 the mode of death was known 40 per cent died of a subsequent attack of coronary thrombosis 35 per cent died instantly 20 per cent died of congestive failure and only 5 per cent of causes unrelated to the heart

Subacute Myocardial Infarction or Necrosis S T *Laufer*[6] (Halifax) describes myocardial necrosis without typical symptoms or an acute onset which can be detected by delayed electrocardiographic changes of coronary occlusion type as subacute myocardial infarction or necrosis Symptoms are often so atypical that the patient may continue his regular activities to his own detriment There are two groups (1) those in patients with manifest signs of heart failure (restlessness gradual fall of blood pressure dyspnea while at rest edema leukocytosis and characteristic cardiographic changes) and (2) those in patients without manifest signs of heart failure (sweating and weakness sometimes accompanied by fever of unknown origin) In a few cases shortness of breath with a brief heavy sensation over the precordium or shortness of breath with palpitation while at rest may be observed The delayed appearance of electrocardiographic changes is in accord with the clinical picture and may only be discovered accidentally some time later Careful history taking is necessary to detect such cases A polymorphonuclear leukocytosis may be the only positive sign

The value of separating the subacute from the acute group of myocardial infarction is that it enables earlier diagnosis and by rest possible prevention of development of the necrosed areas of heart muscle

[Painless myocardial infarction seems to be more common than previously supposed but it is my belief that it is always accompanied by some other subjective symptoms —Ed]

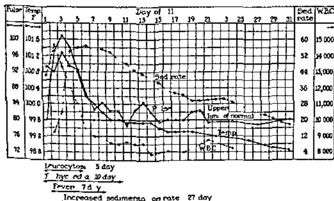
(6) C d M A J 45 36 38 S pt mb 1941

those with minor or unclassified electrocardiographic changes 51 months Survival period for women was *distinctly less than for men 18 3 months as compared to 43 1 months Long survival rates however do occur* among women one woman is still fairly active 15 years after the initial attack and another survived nine years

The survival period was not influenced by subsequent development of angina pectoris which occurred in 63 per cent of patients Congestive failure subsequently *occurred in 28 per cent of the entire group of 372* cases *In 19 per cent it was mild or moderate* and in 9 per cent marked or severe If only those are considered who have already died (101) incidence of decompensation was almost 50 per cent Women suffered from congestive failure more than men Concerning the degree of *recovery from the point of view of physical activity after* the first attack *information was available on 354 cases* 30 per cent returned to essentially full duties 45 per cent to partial duty and 22 per cent to moderately restricted duty and only 3 per cent were completely incapacitated The status of invalidism was apt to grow worse with subsequent *attacks* of coronary occlusion *Those with posterior myocardial infarctions* on the average *ap*peared to have less disability

The age of the patient at initial attack was one of the most important factors in ultimate prognosis The younger patients lived longer had less subsequent angina pectoris *or cardiac decompensation and recovered a greater degree of physical ability* than the older patients Correlating the clinical findings of the acute attack with the course after recovery it appeared that severity of the initial pain bore no relation to the survival period or to the degree of subsequent angina pectoris *The patients with transient auricular fibrillation during* the acute attack seemed to have less subsequent angina pectoris slightly more congestive failure and physical incapacitation but lived at least as long as those without this complication. *A similar statement* can be made *for patients with perica*

Clinical recovery from the attack was good in one third of the patients poor in two fifths and fair in the remainder Two fifths showed no or only slight restriction of physical activity Two thirds complained of precordial pain dyspnea or fatigue and one third had no symptoms of cardiac disability Angina pectoris occurred in three-fifths Coronary occlusion may initiate an anginal syndrome or aggravate one previously present Preexisting angina pectoris may disappear com



F g 96—C l t n f g pul te t mp t ed m t t t d l uk yt n t n 0 f d f t wh h hosp t li t n rr d fi t d y f ll d b rv t w tin d f m th (S ll to t l p 6)

pletely following the attack Presence or absence of angina pectoris was not influenced by the level of blood pressure Dyspnea present in over half the patients was occasionally the only symptom of heart failure or cardiac disability Weakness was common but only rarely occurred in absence of pain or dyspnea Chronic congestive heart failure was present in one fourth of the patients a much lower incidence than during the attack and of a milder degree Persistent diminished amplitude of the heart sounds particularly the first apical sound was observed in about half the patients This sign may be of diagnostic value in subjects over 40 suspected of having coronary disease Gallop rhythm a

Cardiac Infarction Incidence and Correlation of Various Signs, with Remarks on Prognosis Frederick H Shillito, Francis L Chamberlain and Robert L Levy[8] (Columbia Univ) analyzed 50 cases of uncomplicated cardiac infarction as to incidence time of appearance and duration of certain signs Increase in sedimentation rate of the erythrocytes was observed in all but one case Fever occurred invariably other signs were less frequently present Rectal temperature above 104 F leukocyte count higher than 25 000 or venous pressure over 200 mm water indicated grave prognosis Seven of eight patients with any one of these signs died within 16 days after the coronary attack

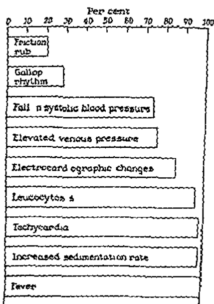


Fig 95—A age n den e of var s gn n 50 f d of r t n

The level of the sedimentation rate is helpful in the differentiation between anginal pain and cardiac infarction It is particularly helpful in infarction with mild symptoms not seen during the first days of illness. Degree of increase is not an index of severity of attack, nor does it serve as guide in prognosis

Follow Up Studies in Coronary Artery Occlusion Arthur M Master Simon Dack and Harry L Jaffe[7] (Mount Sinai Hosp New York City) studied 202 patients who had recovered from acute coronary occlusion one to six years previously

(8) J A M A 118 7 9 Ma 7 194
( ) N w Yo k Stat J M d 42 413 (0 M r 1 194

Physician 32 had symptoms and signs indicating cardiac infarction in the anterior surface of the left ventricle Electrocardiograms (Fig 97) were characteristic temperature was high and remained above normal for six days definite pericardial friction rub was heard and two days later a gallop rhythm Leukocyte count was 16 000 per cu mm with 87 per cent polymorphonuclears

Eleven days after the cardiac infarction the patient developed all signs of an intraventricular clot which had been discharged and was blocking the aorta at its bifurcation

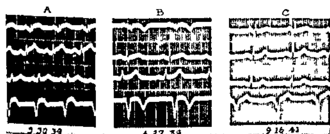


Fig 97 —*A*, elect[illegible] *RST* int[illegible] CF cha act[illegible] CF [illegible] Q wa[illegible] *B* th[illegible] RST [illegible] dev at[illegible] T wa[illegible] CF [illegible] *A* [illegible] *C* [illegible] T w[illegible] Q w[illegible] CF p[illegible]

(Fig 98) Embolectomy was done immediately under local anesthesia A cannula was inserted into the left antecubital vein for intravenous fluid administration blood loss was compensated by transfusions The distal end of the external iliac artery and the proximal portion of the femoral artery of each side were exposed Two fine pieces of rubber tubing were placed beneath the vessels on each side proximal to the origin of the profunda femoris to prevent the clot when dislodged from passing distally and to provide a method for hemostasis When the artery on the right was incised in longitudinal direction a little bleeding occurred from the distal portion of the vessel A modified Babcock vein stripper was inserted proximally until the soft substance of the thrombus was encountered The stripper was then moved up and down to fragment the clot When it was withdrawn free bleeding was obtained A specially prepared catheter the tip of which had been removed and the end carefully smoothed was inserted toward the heart After it had been introduced for about 30 cm suction was applied when withdrawn it car

sign of failing heart was not an uncommon observation

Heart rate and rhythm were normal in most patients Paroxysmal or permanent auricular fibrillation occurred in only five The rarity of arrhythmias in this series is in marked contrast to their frequency in the acute stage of coronary occlusion Hypertension, present in two thirds of the group prior to the acute attack returned or persisted in only one third following recovery Although hypertension did not influence the frequency or severity of angina pectoris or the frequency of subsequent attacks it was more common in those who developed heart failure and in those whose clinical recovery was poor Half the patients resumed their former occupations either full or part time Inability to work was nearly always attributable to an anginal syndrome or heart failure Mild angina pectoris or dyspnea however did not prevent return to work Most patients who resumed work did so within six months after discharge

At least one third of hospital ward patients who recover from acute coronary occlusion may *lead a fairly* active life with no or slight restriction of ordinary activities

Incidence of Chronic Heart Failure (202 Cases)

	No of Cases	%
No heart failure	155	77
Heart failure	47	23
Type		
Left	28	
Right	15	
Left and right	4	
Severity		
Mild	32	
Moderate	14	
Severe	1	

Successful Removal of Saddle Embolus of Aorta 11 Days after Acute Coronary Occlusion I S Ravdin and Francis C Wood[9] (Univ of Pennsylvania) report a case in which use of heparin made possible the successful removal of a large embolus

(9) Ann S rg 114 834 839 November [illegible]

[Prompt diagnosis is life saving in these cases Operation must be performed within six hours —Ed.]

Pericarditis

Pericardiostomy for Suppurative Pericarditis John W Strieder and William R Sandusky[1] (Boston City Hosp) report on 10 cases of suppurative pericarditis treated by pericardiostomy and 28 additional cases collected from the literature

TABLE 1 —Antecedent Disease in Reported and Collected Cases of Suppurative Pericarditis

Antecedent Disease	Cases	Recoveries	Deaths
Pneumonia	13	8	5
Pneumonia with empyema	7	5	2
Empyema	5	3	2
Osteomyelitis	1	0	1
Osteomyelitis and septicemia	2	2	0
Septic arthritis	1	0	1
Suppurative arthritis and septicemia	1	0	1
Metastatic abscesses (hip region and foot joint)	1	0	1
Tuberculous pericarditis	2	0	2
Influenza	1	1	0
Postoperative pneumonectomy for bronchiogenic carcinoma and empyema	1	0	1
Primary pericarditis (?)	1	0	1
Stab wound	1	1	0
Ulcerative colitis and pyemia	1	0	1
Totals	38	20	18

TABLE 2 —Surgical Approach in the Reported and Collected Cases

Approach	Cases		Recoveries		Deaths	
Anterior		29		16		13
Intercostal	1		1		0	
Sternotomy	1		0		1	
One cartilage and part of sternum	1		0		1	
Two cartilages and part of sternum	1		1		0	
One cartilage	6		4		2	
Two cartilages	16		8		8	
Three cartilages	3		2		1	
Posterior		1		1		0
Epigastric		3		2		1
Two-stage epigastric and anterior		1		1		0
Not stated		4		0		4
Totals		38		20		18

(1) New England J Med 317 3 6 Aug 8 1941

ried several masses of clot Free bleeding was prevented by traction on the proximal rubber sling A similar procedure was done on the left side

After much free bleeding the two arteries were closed with arterial silk Just as the suture line in the right femoral *artery was nearing completion 5,000 units of heparin* was introduced intravenously After placing the last arterial suture an additional 5 000 units of heparin was given The wounds were then closed Shortly after operation, a left paravertebral injection with 1 per cent novocain was done

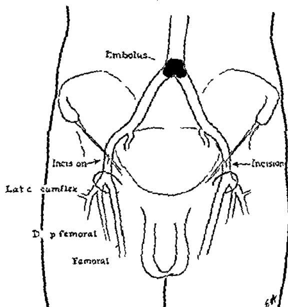


Fig 98—P s t n f mbolu and (n is ns f r ts remo al

Heparin was given for 11 days following operation, by the slow drip intravenous method by adding it to solutions of normal saline and 5 per cent glucose or to 5 per cent glucose alone Coagulation time varied during treatment from 14 minutes to 1 hour and 13 minutes

When discharged the patient had almost normal sensations in both legs, although he still had pain in the dorsum of the left foot, the result of persisting ischemic neuritis Two and a half years later, his lower extremities were perfectly normal musculature was normal and he walked without obvious disability The orthodiagram showed no cardiac enlargement

surgeon's ability to remove enough scar to release the heart on the capacity of the weakened heart muscle to perform its work and on the nonprogression of the inciting disease Prognosis appears to be poor in patients in whom tubercle bacilli can be demonstrated in the pericardial fluid Of 20 patients on whom pericardectomy was performed 13 had a scar of tuberculous origin and 3 a scar resulting from a previous staphylococcus infection Of the 13 7 are living

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PHYSIOLOGIC DIAGNOSIS

Congestive Heart Failure

Value of Combined Measurements of the Venous Pressure and Arm to Tongue and Arm to Lung Circulation Times in Heart Failure Hugh Hudson Hussey Joseph J Wallace and John C Sullivan[4] (Georgetown Univ) report results of simultaneous measurements in 100 consecutive cases of heart failure Etiologic classification of the cases is given in the table

Etiologic Classification of Cases of Heart Failure

D n is	N Ca es
Rheumatic heart disease	13
Hypertensive heart disease	57
Syphilitic heart disease	14
Coronary arteriosclerosis	8
Hyperthyroid heart disease	3
Beriberi heart disease	2
Heart disease due to anemia	1
Undetermined etiology	2
Total	100

The results show that in general heart failure the venous pressure is abnormally elevated or undergoes a significant rise when the abdomen is compressed and that circulation times are usually prolonged When improvement occurs in this type the arm to tongue circulation time may nevertheless remain prolonged for an

(4) Am H rt J 3 22 36 J nu ry 194

Suppurative pericarditis is not rare as demonstrated by autopsy figures Diagnosis is missed frequently because the condition is obscured by concomitant thoracic disease In untreated cases mortality approaches 100 per cent while with pericardiostomy the treatment of choice it is 50 per cent Further reduction should be obtained with chemotherapy supplementary to pericardiostomy Operation should be done early to achieve optimal surgical conditions and probable further lowering of mortality Such a policy may involve operating on a certain number of patients in whom the diagnosis cannot be proved by pericardicentesis and even in a few in whom organisms cannot be found in the fluid obtained by early pericardicentesis

Chronic Pericardial Disease Alfred Blalock (Vanderbilt Univ) and C Sidney Burwell (Harvard Univ)[2] present an extensive evaluation of findings in 28 cases of constrictive pericarditis Symptoms and signs observed in these cases are shown in the table Pericardectomy was the treatment of choice In considering indications for and the time of operation it must be remembered that successful therapy is dependent on the

SYMPTOMS AND SIGNS IN 28 CASES OF UNDOUBTED CONSTRICTIVE PERICARDITIS

	%
Distended veins	100
Increased venous pressure (180 390 mm H)	100
Enlarged liver	100
Edema (peripheral)	96
Tachycardia	100
Diminished pulsation (fluoroscope)	100
Paradoxical pulse	93
Low pulse pressure	93
Faint heart sounds	86
Ascites	89
Pleural effusion	86
Greatly enlarged heart	0
Pulmonary edema (gross)	0
Hypertension	0
Valvular disease	0
Systolic retractions	0
Auricular fibrillation	4
Paroxysmal dyspnea	4

(2) Surg Gynec & Obst 3 433 461 October 1

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The results show that in general heart failure the venous *pressure is abnormally elevated or undergoes* a significant rise when the abdomen is compressed and that circulation times are usually prolonged When improvement occurs in this type the arm to-tongue circulation time may nevertheless remain prolonged for an

(4) Am Heart J 3 2 6 January 194

Suppurative pericarditis is not rare, as demonstrated by autopsy figures Diagnosis is missed frequently because the condition is obscured by concomitant thoracic disease In untreated cases mortality approaches 100 per cent while with pericardiostomy, the treatment of choice it is 50 per cent Further reduction should be obtained with chemotherapy supplementary to pericardiostomy Operation should be done early to achieve optimal surgical conditions and probable further lowering of mortality Such a policy may involve operating on a certain number of patients in whom the diagnosis cannot be proved by pericardicentesis and even in a few in whom organisms cannot be found in the fluid obtained by early pericardicentesis

Chronic Pericardial Disease Alfred Blalock (Vanderbilt Univ) and C Sidney Burwell (Harvard Univ) present an extensive evaluation of findings in 28 cases of constrictive pericarditis Symptoms and signs observed in these cases are shown in the table Pericardectomy was the treatment of choice In considering indications for and the time of operation it must be remembered that successful therapy is dependent on the

Symptoms and Signs in 28 Cases of Undoubted Constrictive Pericarditis

Distended veins	100
Increased venous pressure (180-300 mm H)	100
Enlarged liver	100
Edema (peripheral)	96
Tachycardia	100
Diminished pulsation (fluoroscope)	100
Paradoxical pulse	93
Low pulse pressure	93
Faint heart sounds	86
Ascites	84
Pleural effusion	86
Greatly enlarged heart	0
Pulmonary edema (gross)	0
Hypertension	0
Valvular disease	0
Systolic retractions	0
Auricular fibrillation	4
Paroxysmal dyspnea	4

(2) Surg Gynec & Obst 73 433 461 October

A method of measuring the pulmonary arterial and venous pressures in patients by a painless precise and nonperilous procedure would be of great help

[Nocturnal dyspnea is one of the first manifestations —Ed]

Congestive Heart Failure Factors Influencing Ultimate Prognosis T J Dry[6] studied 150 patients with congestive cardiac failure to ascertain what factors if any might influence the course of patients whose hearts had been decompensated The patients were unselected and thus were a fair cross-section of such individuals Measures for restoration of cardiac function included digitalis and diuretics of various kinds either individually or in combination restriction of fluid and salt and the outlining of a protective regimen after the patient had become ambulatory All patients were urged strongly to establish contact with the family physician early so that recurrence of failure could be treated promptly

Causation of congestive heart failure was considered to be on the basis of hypertension and coronary disease either independent of or in association with each other in 114 patients of rheumatic heart disease in 24 and of hyperthyroidism in 7 Syphilitic aortitis was diag nosed in three patients and in two decompensation was thought to be due to obesity although both were at the age when coronary disease is common Most patients were between 50 and 69 and there were 106 men and 44 women

At completion of the study only 22 of the 150 patients were alive Figure 99 presents a survival curve Of the entire group 40 survived five years or longer and 110 died within five years after the first break in cardiac compensation The table summarizes the significant data relative to these two groups Among those who lived five years or more were a greater proportion of persons in the earlier decades of life a greater propor tion of women and a greater proportion of patients with

(6) I St ff M t M y Cl 17 55 59 Ja 8 194

unpredictable period after all other signs of heart failure have disappeared This presumably indicates persistence of left ventricular failure In seven cases clinical observations indicated isolated left ventricular failure during the entire time the patients were observed Venous pressure and arm to lung circulation time were normal but the arm to tongue circulation time was prolonged In 34 cases the lung to-tongue circulation time was within normal limits This tends to impair the value of this measurement in diagnosis of isolated right ventricular failure

The venous pressure may be abnormally high or rise significantly with abdominal compression when other signs of failure of the right ventricle are lacking Repeated measurements of venous pressure and circulation time afford a means of following the course of the disease objectively Combined measurements of venous pressure and circulation time are necessary for perfect diagnostic appraisal of heart failure When there are symptoms suggestive of heart failure but none is actually present the circulation measurements are as valuable in ruling it out as they are in diagnosing and studying the condition

Pathologic Physiology of Early Manifestations of Left Ventricular Failure C Sidney Burwell[5] (Harvard Univ) emphasizes that left ventricular failure is frequent and dangerous and in its early stages is often pure i e without associated failure of the right ventricle These early stages are commonly seen in offices or outpatient departments rather than in wards Diagnosis of heart failure does not require high systemic venous pressure an enlarged liver or peripheral edema but may be made on the evidence of isolated failure of the left ventricle Early evidences of such failure include gallop rhythm diminished vital capacity prolonged pulmonary circulation time roentgen evidence of pulmonary congestion and various types of dyspnea

(5) A n I i Med 16 104 11 J u ry]

to depend on systematic supervision of the patient and an indefinite extension of a therapeutic program intended to meet recurrences of cardiac failure Thus the analysis indicates that the after care of a patient with restored compensation after the first episode of congestive heart failure is one of the more important factors in prolonga tion of life

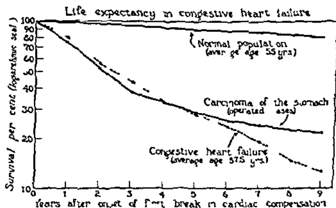
COMPARISON OF PATIENTS WHO SURVIVED FIVE YEARS OR MORE WITH THO E WHO DIED WITHIN FIVE YEARS OF ONSET OF CONGESTIVE HEART FAILURE

	L ss Th n 5 Yr (110 Patient)		5 Yr o M (40 Pa ients)	
	C ses	%	Cases	%
45 yr old or less	15	14	11	28
Proportion of women	14	13	12	30
Proportion of rheumatic heart disease	30	27	14	35
Proportion of coronary disease or hypertension or both	92	84	25	62
Significant ECG findings (all types)	96	87	31	78
Auricular fibrillation	36	33	17	42
Significant T wave changes	79	72	20	50
Conduction defects (all types)	29	26	5	12
Essentially normal ECG	14	13	9	22
Cardiac enlargement				
Grade 3 or 4	57	52	21	52
Grade 2	39	36	12	30
Grade 1	8	7	3	8
Grade 0	6	5	4	10

Oral Administration of a Mercurial Diuretic in Treatment of Congestive Heart Failure K L Dickens[7] (Louisiana State Univ) treated nine patients with con gestive heart failure on an arteriosclerotic hypertensive or syphilitic basis with salyrgan theophylline orally The drug is described by the manufacturers as a com bination of salyrgan and theophylline in the ratio of 2 1 It was supplied in enteric coated tablets each con taining 80 mg salyrgan and 40 mg theophylline (under

(7) New O l M & S J 94 344 345 J u y 194

rheumatic heart disease than among those who lived less than five years Aortic lesions are better tolerated than mitral stenosis so that there is a tendency for congestive heart failure to supervene earlier in patients with mitral disease than in those with rheumatic aortic lesions Compensation once restored is maintained poorly by patients with rheumatic aortic lesions in contrast with those with mitral stenosis who may respond satisfactorily to treatment through repeated episodes of



F g 99—Surv al cu es f pat t w th cong sti e h art f lu e f normal p pulati n nd fo pat e ts w th c t r ci n f re n ma f the t mach Last survi al is based on stud s by Walt rs nd asso at (np bl hed d t)

recurrent congestive heart failure The poor outlook in syphilitic aortitis associated with congestive heart failure is well known

Examination of the records of the 25 patients still alive showed a high incidence of rheumatic heart disease In almost every case there was cardiac enlargement varying from moderate to gross hypertrophy at the original examination In 50 per cent of the cases the hearts were fibrillating at the time of treatment for heart failure, and gross electrocardiographic abnormalities existed in almost every case Only a few patients were living an approximately normal life prolongation of life seemed

Anginal Syndrome

Diagnosis of Coronary Artery Disease H M Marvin[8] (Yale Univ) discusses the criteria by which the physician may suspect or recognize structural changes in the coronary arteries that interfere with the heart s nutrition sufficiently to be of consequence to the patient Clinical evidence pointing to coronary arteriosclerosis consists of a clear history of anginal heart failure in the absence of other causes occurrence of acute myocardial infarction or presence of congestive heart failure if other types of heart disease and vitamin deficiency are excluded The typical and unmistakable anginal pain should be regarded as evidence that the coronary blood flow is inadequate for the needs of the heart muscle and that this inadequacy is due in most cases to arteriosclerotic narrowing or closure of the vessels although typical anginal pain may occur with normal coronary *arteries in severe anemia or during prolonged paroxysms* of tachycardia with excessive ventricular rates Concerning roentgen evidence coronary arteriosclerosis is present if calcification of the vessels can be demonstrated if there is a ventricular aneurysm or if localized reversal of ventricular pulsation is revealed by fluoroscopic examination

Concerning electrocardiographic evidence the S T segment and T wave have caused more confusion and trouble than any other portion of the tracings Depression or elevation of the S T junction or segment and inversion of the T wave are apparently more generally accepted than any other changes in the electrocardiogram as indications of heart disease and especially of coronary *arteriosclerosis Whether or not this statement* is justified can be judged by the following quotation from Sprague Without the hope of its being complete the following list of conditions other than coronary atherosclerosis responsible for abnormalities of S T and T segments is submitted

(8) N w E gl d J Med 226 1 4 F b 12 1942

the research number of S T O 3813 by the Winthrop Chemical Company Incorporated)

Before administration each patient was placed at complete bed rest given digitalis with sedation, limitation of fluids salt free diet and ammonium chloride (3 Gm daily) Fluids were limited to about 1 000 cc daily Urinary output was determined both while the patients were on the preliminary drugs and during administration of the diuretic Weights were determined on admission and discharge When the diuretic was given ammonium chloride dosage was reduced to 2 Gm daily A single dose of 5 tablets of salyrgan theophylline was given after breakfast usually between 9 00 and 10 00 a m this dose was repeated usually in four to six days As many as three courses were given without deleterious effects Dosage and diuretic effects obtained are shown in the table

EFFECTS OF SALYRGAN THEOPHYLLINE GIVEN ORALLY

Patient	Weight Lb			Urinary Output Av		Total Dosage Tablets	Days Treated
	Before	After	Loss	NH_4Cl Only Cc	NH_4Cl plus Drug Cc		
1	170	[illegible]	15	900	2 [illegible]00	10	19
2	164	151	13	800	1 200	10	25
3	155	149	6	1 [illegible]00	2 000	5	20
4	156	144	12	450	1 044	1[illegible]	19
5	152	133	19	750	2 400	10	7
6	168	145	23	900	2 225	10	12
7	137	131	6	500	1 309	10	10
8	204	198	6	1 000	1 [illegible]00	15	15
9	160	145	15	700	1 800	10	12

Contraindications to use of the diuretic are the same as to any mercurial preparation i e, acute nephritis, colitis with melena chronic renal disease, low or fixed specific gravity of the urine and nitrogen retention in the blood Otherwise the diuretic is a safe and efficacious drug for promotion of diuresis in edema from congestive heart failure

Pain in Coronary Arteriosclerotic Disease of the Heart Basil Blumenthal and John A Reisinger[9] (Washington, D C) report a study of the painful manifestations in 60 patients with coronary arteriosclerotic disease of the heart There is great variation in the symptoms although the symptom complex presents characteristics that usually permit differentiation if detailed history is obtained The pain always involves the mid line of the chest or abdomen at some time but is not *usually limited to this region Pain localized in the* mammary region or laterally to the parasternal lines should not be considered as evidence of the anginal syndrome or myocardial infarction until proved otherwise The character of the pain is most often squeezing oppressive or burning but this alone is not consistent enough for differentiation In some cases the patient s complaint is more of discomfort than pain Of the group 42 per cent of patients described the pain as crushing tightness squeezing constrictive like a vise oppressive gripping and pressing 20 per cent described it as burning *hot* like heart burn like a hot iron like hot coals 10 per cent termed it swelling a lump fulness expansion 8 per cent called it sharp cutting and like a knife and another 8 per cent considered it as grinding indescribable like running a mile and crampy while 12 per cent described it as just aching Radiation of the pain does not always occur and its distribution is not pathognomonic The sensation of numbness and fatigue in the arms approaching a paresis is often striking

The stimulus to elicit pain is of greatest importance since diagnosis of the anginal syndrome should depend on *demonstration of a definite relation between activities* increasing the heart work and onset of pain The following tabulation summarizes the activity of the patients at the time of onset of an attack.

In myocardial infarction pain may or may not follow a recognizable stimulus but in most cases the latter will

(9) M B U Vet Adm 18 166172 Oct 1941

1 Drugs
   Digitalis
   Quinidine
   Tobacco
2 Myocardial infection
   Rheumatism
   Diphtheria
   Trichinosis
3 Other general infections
   Pneumonia
4 Pericarditis
5 Toxemia and metabolic disorders
   Uremia
   Diabetic acidosis
   Hypocalcemia
   Hyperthyroidism
   Hypothyroidism
   Insulin shock
   Addison s disease
   Anemia
   Avitaminosis especially beriberi
   Acidosis
   Alkalosis
   Anoxemia
   Shock
6 Changes in posture of the patient
7 Axis deviation
8 Abnormal heart rhythms
   Paroxysmal tachycardia and auricular fibrillation
   Sinus tachycardia
9 Alterations in vagosympathetic tone
   Pain
   Fear
   Anesthesia
10 Pulmonary embolism
11 Miscellaneous
   Periarteritis nodosa
   Trauma
   Malignancy of myocardium
   Dissecting aneurysm of coronary artery
   Dissecting aneurysm of aorta
   Syphilis of aorta
   Gallbladder disease
   Scleroderma
   General anasarca
   Cooling the heart through ingestion of ice water
   Terminal states of all kinds
   Unexplained

This list contains 41 different conditions 33 of which do not imply heart disease Marvin states that undoubtedly changes in these segments are found with coronary atherosclerosis but coronary disease is only one of many factors that cause such changes and it is definitely impossible to decide from the electrocardiogram alone which of these many causes is responsible Summarized in one sentence, this would say if myocardial infarction is excluded there is no change in the electrocardiogram that in itself justifies the diagnosis of coronary disease because the alterations on which this diagnosis is based may be and often are due to other causes

[Again I should like to stress the importance of giving the cardiologist a complete clinical picture before expecting him to make a satisfactory electrocardiographic diagnosis.—Ed.]

the T wave in lead IVF regardless of RS T deviation and (4) partial reversal of direction of T wave in lead IVF, accompanied by an RS T deviation of 1 mm or more in this lead The test must not be performed in

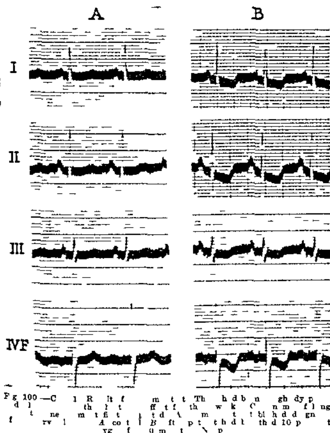


Fig 100 —C l R lt f m t t Th h d b n gh dy p d l th l t ff t f th w k C n m f l ng t ne m t fi t t d m t t bl h d d gn f rv l A co t l B ft p t t h d l th d 10 p t yg f 0 m t p

presence of congestive heart failure within four months after known cardiac infarction or on the same patient more than once in 24 hours With these precautions serious reactions are avoided

be true Pain should be relieved shortly after the stimulus causing it has passed Persistent pain of a constant character with remissions over days or weeks strongly indicates the probability of a myocardial infarction

RESTING

Lying on couch or bed	12
Asleep	4
Sitting quietly	12
	8

(7 were resting after a meal)

MODERATE EXERTION (PHYSICAL OR MENTAL)

Bathing	1
At a party	1
Playing cards	2
Walking on level	7
Driving auto	2
	13

DURING OR IMMEDIATELY FOLLOWING SEVERE EXERTION OR MENTAL STRAIN

During heavy work	6
Immediately after heavy work plus severe nervous strain	3
	9
Lying in bed postoperative	1
Unknown	2

Thus cardiac pain caused by obliterative disease of the coronary arteries has certain clinical features of use in differential diagnosis Careful history taking is of great est necessity

Anoxemia Test as Index of Coronary Reserve Robert L Levy James L Patterson Thomas W Clark and Howard G Bruenn[1] (Columbia Univ) report serial observations on 137 patients and their application to the detection and clinical course of coronary insufficiency The criteria of positive reaction were (1) the arithmetical sum of the RS T deviations in all four leads totals 3 mm or more (2) there is partial or complete reversal of the direction of the T wave in lead I accompanied by an RS T deviation of 1 mm or more in this lead (3) there is complete reversal of the direction of

(1) J A M A 11 2113 2119 Dec 0 1941

The test is helpful in differentiating conditions producing pain in the chest When positive the reaction serves to distinguish discomfort due to coronary insufficiency from that caused by other disorders It is useful in following variations in the coronary reserve and so in appraising the efficiency of the coronary circulation at the time of its performance Serial observations reflect in a general way the trend of the clinical course The test does not permit prediction of future occurrence of coronary occlusion It affords an index within undefined limits of the adequacy of the coronary blood flow but yields no information as to nature or extent of the pathologic lesions in the heart

***Angina Pectoris Significant Electrocardiographic* Changes Following Exercise** Arthur Twiss and Maurice Sokolow[1] (Univ of California) induced coronary insufficiency with a standard exercise test and took four lead electrocardiograms during the induced attack to determine any possible objective criteria for diagnosis of angina pectoris They found that objective evidence of angina pectoris can be obtained from electrocardiographic changes in two thirds of all cases if the pain is reproduced by exercise and in only one third if the pain is not reproduced by exercise Significant changes electrocardiographically developed after exercise in 56 per cent of patients with angina pectoris irrespective of absence or presence of pain These changes were S T segment depression or elevation of 1 mm or more in lead I of 1 5 mm or more in lead II of 1 5 mm or more in lead III and 2 mm or more in lead IV conversion of an upright to a diphasic or inverted T wave took place in leads I II or IV and development of bundle branch block occurred If any one of these changes occurred the electrocardiogram was considered abnormal Use of the chest lead increases the number of abnormal curves by about 20 per cent

The authors emphasize that changes caused by exercise offer objective evidence of angina pectoris but a

(1) Am H t J 3 498 51 Ap il, 194

A positive reaction was not observed in any patient without cardiac disease or severe anemia A positive reaction may be regarded as a sign of coronary insufficiency but a negative reaction does not exclude disease of the coronary arteries Pain during a test with negative result particularly if it appears during the first 10 minutes of induced anoxemia affords presumptive evidence of diminished coronary reserve and the patient should be carefully observed for further signs of coronary disease and managed conservatively

TABLE 1 — MATERIAL

No of patients		13[illegible]
No of tests		[illegible]
Duration of follow up study 6–39 months (av 21)		
Clinical diagnoses		
Person normal		[illegible]5
Suspected coronary sclerosis		[illegible]4
Coronary sclerosis		67
No known infarction	45	
Healed infarction	[illegible]2	
Hypertension		10
Miscellaneous		11
Rheumatic heart disease	5	
Syphilitic aortic insufficiency	3	
Anemia	2	
Pericarditis	1	

TABLE 2 — RESULTS OF TEST IN RELATION TO CLINICAL COURSE IN 67 PATIENTS WITH CORONARY SCLEROSI

Result of First Test	Cases	Result of Follow Up Test Positive		Complications During Observation	Deaths	Complications + Deaths	
		N	%			No.	%
Positive	30	19	66 3	3	4	7	23 3
Negative with pain	14	4	28 6	1	2	3	21 4
Positive + negative with pain	44	23	[illegible]2 3	4	6	10	[illegible]2 7
Negative no pain	23	6	26 1	1 †	1 †	1	4 3

Coronary occlusion, pulmonary ed ma [illegible]
† Same patient.

DEATH RATES BY AGE FROM ANGINA PECTORIS AND CORONARY DISEASE AND STANDARDIZED DEATH RATES FOR AGES OVER 45 IN CERTAIN OCCUPATIONS ENGLAND AND WALES 1930–1932

Occupational Group	Population	Average Annual Death Rate per 100 000					Standardized Rate 45 and Over
		45–54	55–64	65–74	75 and Over	45 and Over	
Agricultural and gardeners laborers	271 737	7.8	25.9	71.1	116.6	38.3	31.6
Coal hewers and getters	157 251	15.2	52.4	90.7	101.3	42.6	46.2
General laborers	491 845	23.4	50.3	108.6	156.7	53.0	55.4
Builders plasterers bricklayers and masons laborers	51 079	29.8	50.6	122.1	298.3	57.6	69.1
Road transport motor drivers	63 473	24.7	83.8	175.1	192.6	50.4	81.1
Railway engine drivers	31 415	21.4	88.8	234.3	130.6	85.9	88.2
Fitters mechanics and tool makers	106 671	39.3	84.[illegible]	175.2	215.1	80.6	89.1
Commercial travelers	50 813	49.0	105.4	285.1	405.7	116.1	131.0
Typists and other clerks (not civil service)	147 751	45.0	115.9	290.0	364.0	1[illegible]0.5	131.2
Bank and insurance officials	3 635	42.9	159.4	413.6	486.2	160.8	174.0
Clergymen except Roman Catholic priests	24 742	46.9	180.2	475.6	393.6	234.4	188.3
Managers in certain occupations	134 388	49.9	155.9	441.2	892.8	183.8	200.9
Wholesale proprietors	43 295	59.5	19[illegible].7	515.7	617.1	214.8	218.3
Judges barristers and solicitors	13 606	37.6	155.6	565.5	787.4	307.6	241.5
Physicians and surgeons	16 009	80.0	313.0	628.9	875.9	343.6	209.6

normal response does *not* on the *other hand, rule out* the presence of coronary insufficiency (angina pectoris)

Coronary Disease and Occupation Frank G Pedley (McGill Univ) discusses the separate classification of diseases of the coronary arteries the sex incidence and color ratio of coronary disease and refers to the occupational mortality figures published by the Registrar General of England and Wales The latest publication deals with the experience in 1930 to 1932 The mortality by ages is given in many occupational groups and the occupied and retired population is grouped into five major social groups in a descending economic scale Group 1 represents the highest economic class and group 5 the lowest For all age groups *group 1 shows a far higher death rate than does the lowest economic group* Data *in connection* with 15 specific occupational groups are given in the table These groups were selected at *random from nearly 90* occupational classifications The *data are the averages* of three years The figures are *definitely* impressive The Registrar General states

> The figures seem to show that general cardiovascular failure is more likely to occur without anginal symptoms among those *engaged in* manual occupations but whether this is due to the coronary arteries being maintained in a more healthy condition or to the greater demands made on the heart by physical exertion or to nervous, dietary or other peculiarities associated with professional or sedentary occupations is a matter for surmise The fact that women are relatively less liable to angina pectoris than to the other categories of degenerative heart disease makes it appear doubtful whether a sedentary form of occupation is an important factor in producing the high angina rates in classes 1 and 2

The assumption that women lead sedentary lives is probably debatable

The high incidence of coronary disease among the members of *the higher* economic groups has been attributed by some authors to nervous strain This hypothesis might be developed on a rational basis for the influence of the nervous system and the emotions on the

(1) C ad M A J 46 147-151 Feb ry 194

Death Rates by Age from Angina Pectoris and Coronary Disease and Standardized Death Rates for Ages over 45 in Certain Occupations England and Wales 1930–1932

Occupational Group	Population	Average Annual Death Rate per 100 000					Standardized Rate 45 and Over
		45–54	55–64	65–74	75 and Over	45 and Over	
Agricultural and gardeners laborers	291 737	7 8	25 9	71 1	116 6	38 3	31 6
Coal hewers and getters	157 281	15 2	52 4	90 7	109 3	42 6	46 2
General laborers	490 848	23 4	50 3	108 6	156 7	53 0	55 4
Builders plasterers bricklayers and masons laborers	51 029	20 5	50 6	122 1	208 3	57 6	69 1
Road transport motor drivers	63 473	24 7	83 8	175 1	192 6	50 4	81 1
Railway engine drivers	31 415	21 4	88 8	234 3	130 6	85 9	88 2
Fitters mechanics and tool maker	106 671	39 3	84 3	175 2	215 1	80 6	83 1
Commercial travelers	50 813	49 0	105 4	285 1	405 7	116 1	131 0
Typists and other clerks (not civil service)	147 751	45 0	115 9	290 0	364 0	120 5	131 2
Bank and insurance officials	93 635	42 9	159 4	413 6	456 2	160 8	174 0
Clergymen except Roman Catholic priests	24 742	46 9	180 2	475 6	503 6	234 4	188 3
Managers in certain occupations	131 358	49 9	155 9	441 2	822 8	163 8	200 3
Wholesale proprietors	43 295	53 5	192 7	515 7	617 1	214 8	218 3
Judges barristers and solicitors	13 656	97 6	155 6	65 5	787 4	307 6	241 5
Physicians and surgeons	16 009	80 0	313 0	628 9	825 3	343 6	299 6

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The assumption that women lead sedentary lives is probably debatable

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(2) Canad M A J 46 147 1 1 F br ry 194

pendent on good cardiac function and that failure or impending failure of the circulation is often first manifested by gastro intestinal symptoms Gastro intestinal manifestations of heart disease include epigastric pain abdominal distress right upper quadrant pain vomiting nausea belching diarrhea obstipation flatulence dysphagia hiccup and hematemesis Epigastric pain the most frequent symptom may vary from mild sensation of fulness to severe excruciating pain and is generally not related to meals The distress may be due to acute congestion of the liver from right ventricular failure or to coronary disease

Jaundice may be due to heart failure either produced by impairment of liver function increase in the production of bilirubin or diminution in blood flow through the liver But even the presence of jaundice in heart failure does not indicate organic liver disease It is questionable whether disease of the gastro intestinal tract can produce chronic myocardial changes in a previously normal heart but an existing chronic myocardial state may be aggravated particularly by gall bladder disease Diseases of the esophagus may produce symptoms and pain which make the diagnosis of cardiac disease difficult on occasion One differential factor is that coronary pain is invariably precipitated by effort whereas esophageal pain is more often associated with eating

RESPONSE TO VARIOUS FACTORS IN DIAPHRAGMATIC HERNIA AND HEART DISEASE

	Diaphragmatic Hernia	Heart Disease
Exercise	Inconstant	Usually aggravate
Horizontal position	Usually aggravates	Little or none
Large meal	Almost always aggravates	Variable
Alcohol	Aggravates	Relieves
Tobacco	Aggravates	Aggravates
Hematemesis	Frequent	Never
Nitroglycerin, Rest, Small meals, Belching	Usually relieves	Usually relieves
Atrophine	May relieve	None
Alkali	May relieve	May relieve

heart is well recognized But no direct relation between emotional strain and coronary disease has as yet been found

Pedley concludes that lacking proof to the contrary coronary disease is actually increasing and that it is a disease peculiarly associated with high pressure intel lectual activity and probably low pressure or spasmodically regulated physical activity The association if actually true does also suggest that the individual in the dangerous occupation might well consider a rever sion to a more physiological way of living

Favorable Prognosis of Coronary Disease Drew Luten[3] (St Louis) reports a number of cases of cor onary disease which illustrate the fact that usefulness and activity of the individual concerned need not en tirely or even to a large degree cease because of the illness A large share of worthwhile work is being done by those who have angina pectoris of greater or less degree and by individuals with an unquestioned his tory of coronary thrombosis Careful attention by the physician to his attitude and to the specific directions given will often enable the patients to do their work better and for more years and will also lighten the cloud under which many of them live It may also lessen the tension and anxiety which in many cases are contribu tory to unhappy episodes Just how great is the thera peutic value of cheerfulness perhaps can never precisely be determined But in the therapy of mental pain, no excuse can be offered for failure to use the one sure agent cheerful optimism The words of Parkinson should be remembered namely that too much stress has been laid on the gravity of angina pectoris and too much attention has been centered on the anginal death and too little on the anginal life and its management

Interrelationship of Gastro Intestinal and Cardiac Disease M D Hargrove[4] (Shreveport La) states that good function of the gastro intestinal tract is de

(3) Illinois M J 81 52 56 Jan ry 194
(4) New Orleans M & S J 94 111 117 Sept mbe 1941

of attacks of anginal pain at times and of pain due to esophageal spasm at others led the authors to study roentgenographically the esophagus of patients with attacks of substernal pain particularly those supposed to be anginal but not provoked by effort

Esophageal spasm was a common disorder in the patients studied In many it was entirely asymptomatic In others however it produced substernal pain which so far as the patient s description was concerned was indistinguishable from the pain of angina pectoris or in the more prolonged attacks acute coronary occlusion In patients with pain during esophageal spasm the esophagus must be examined roentgenographically during attacks of pain to discover the spasm At other times it may show no spasm so that if examination is made with the patient free from pain the diagnosis will be missed In some patients the spasm seems to be persistent and the pain intermittent This pain which may have the same distribution and radiation as anginal pain may be mild or it may be severe enough to cause marked pallor sweating or even collapse Opiates may be required It differs from anginal pain however in that in some cases a history of difficulty in swallowing during the pain attack can be elicited The seizures seem not to be provoked by exertion The pain is usually not relieved by nitroglycerin in any way comparable to the relief obtained in angina pectoris but is often improved in time by antispasmodics sedatives and psychotherapy The electrocardiogram during the attack remains normal

In studies of the esophagus of patients during attacks of anginal pain both induced and spontaneous no spasm could be observed If electrocardiograms with multiple chest leads are made during pain a considerable proportion show significant changes Thus angina pectoris and esophageal spasm bear no close relation to each other except for the similarity of the pain and the fact that rarely each may occur at different times in the same patient Angina pectoris does not seem to

Diaphragmatic hernia of any type, and particularly hiatus hernia may be confused with coronary disease Symptoms of hiatus hernia include dyspnea, cyanosis palpitation feeling of fulness or of suffocation and sub sternal pain which may radiate to the shoulder Points in differential diagnosis are summarized in the table

Differential Diagnosis of Angina Pectoris with Special Reference to Esophageal Spasm and Coronary Occlusion Charles C Wolferth and Joseph Edeiken[5] (Univ of Pennsylvania) discuss the differential diagnosis between the anginal syndrome and various non cardiac conditions A partial list of the problems of differential diagnosis includes pleurisy pleural adhesions *myositis in various muscles of the chest shoulders arms* or neck skeletal muscle strains neuralgia neuritis root pains cervical rib the scalenus anticus syndrome cord tumor herpes zoster spondylitis substernal thyroid aortitis aortic aneurysm various types of mediastinal inflammation especially pericarditis neoplasms, eventration of the diaphragm hiatus hernia the precordial or substernal aches or pains of hypertension and the precordial aches of (1) valvular disease (2) fatigue (3) nervous strain or psychoneurosis (4) toxic states such as hyperthyroidism or excessive use of tobacco digestive disturbances such as flatulence hyperacidity peptic ulcer pylorospasm or spasm of the colon and biliary tract disease The most important of all conditions is esophageal spasm which presents an urgent and difficult problem more frequently than any other

Esophageal spasm is not uncommon and is capable of producing various symptoms such as difficulty in swallowing and substernal pain or distress The opinion has been expressed that the pain of what is called angina pectoris is in reality produced by spasmodic contraction of the esophagus and stomach Morrison and Swalm induced what they believed to be attacks of angina pectoris by inflating balloons in the esophagus and thereby producing *distention Occurrence in a patient*

(5) P n syl an a M J 45 579 584, M h, 1942

subsequent ligation of the descending branch of the left coronary artery One important feature of these compensatory mechanisms appears to be a rise in arterial pressure in the vascular field drained by the occluded vein This field is the whole apical region where most *of the arteriosclerotic disease producing pain is found* These results therefore suggested that venous ligation would be of considerable value in treatment of human advanced coronary disease A patient with severe angina of effort operated on in 1939 has been free from pain for more than two years

Man 54 *had for five years had pain in the midsternal* region, occurring on exertion or excitement, never longer than five minutes duration except on one occasion At admission (1939) he was unable to walk slowly for more than 100 yd on the level without pain The pain could be induced by swallowing cold water Rest and paravertebral injections of alcohol brought no relief One attack lasted for three hours but the character and frequency of the following attacks did not change

The patient was well nourished and of good color and nutrition Pulse rate and temperature were normal and blood pressure was 150/80 There was no cardiac enlargement the heart sounds were distant and a soft systolic murmur was heard at the pulmonic area Electrocardiograms taken May 1936 and December 1937 showed that at some time between these dates an anterior coronary occlusion had occurred although no satisfactory clinical history could be obtained The tracing on admission showed a slight prolongation of auriculoventricular conduction a diphasic T iso electric T and negative T with widening of the QRS complexes This was characteristic of an old myocardial infarction The patient was kept in bed for four weeks and had only one attack of anginal pain during this time

Quinidine was *given to prevent ventricular* fibrillation during operation A transverse incision was made from the mid sternal line along the second left intercostal space the fibers of the pectoralis major being separated by blunt dissection Portions of the second and third ribs with their cartilages were excised through this incision The normal left lung and pleura were exposed with the tissues of the anterior mediastinum immediately under the edge of the sternum With blunt gauze dissection *the pleura and left lung were gradually* pushed laterally so as to give access to the heart A small tear in the pleura was ligated The pericardium was incised vertically

time and later revert to normal despite continuance of the anginal seizures Such changes suggest occlusion of a vessel with minor degenerative changes in the heart muscle

Treatment of Angina Pectoris with Testosterone Propionate Maurice A Lesser[6] (Massachusetts Gen l Hosp) treated 24 patients with a clearly established diagnosis of angina pectoris 20 were men Ages varied from 40 to 77 Intramuscular injections of 25 mg *every second to fifth day* for a total of 5 to 25 injections, with an average of 11 injections were given Favorable results were *obtained in all Frequency severity* and duration of attacks diminished, and physical activities could be increased considerably without precipitating attacks Beneficial effects persisted 2 12 months after discontinuing treatment Improvement in the men was greater No appreciable improvement followed control injections of plain sesame oil although the same patients' *responded when placed on testosterone propionate ther* apy No untoward effects were observed Fluoroscopic examinations serial kymograms and electrocardiograms showed no uniform changes with this therapy Thus ap parently the drug is a valuable aid in treatment of this condition and warrants further investigation

Treatment of Angina Pectoris of Atheromatous Ori gin by Ligation of the Great Cardiac Vein Mercier Fauteux and J H Palmer[7] (McGill Univ) recall ex perimental studies on dogs made in *1935* on the assump tion that ischemia of the myocardium resulting from arteriosclerosis (atheroma) of the coronary arteries was not essentially different from that caused in the extremi ties by the same disease It was hoped that surgical *procedures* which had been of value in treating diseases of the limbs might also be used for coronary sclerosis One of the results was *to show that after the great cor* onary vein had been ligated circulatory readjustments occurred in the coronary system permitting *survival of*

(6) New England J Med 26 51 54 Jan 8 19'
(7) Canad. M A J 45 95 298 October 1941

in an atheromatous but still patent coronary artery There is however experimental evidence that previous ligation will by bringing about changes in the vascular bed prevent the formation or at least limit the size of an infarct when the coronary artery is later tied off and will under these circumstances prevent sudden death This strongly suggests that the operation may find a place in compensating beforehand for a future *coronary occlusion*

The result in this case was so encouraging that since then five more patients with severe angina pectoris have been operated on but the postoperative period of observation is too short to permit conclusions

Principles Underlying Treatment and Management of Coronary Disease Frederick A Willius[8] (Mayo Clinic) states that coronary disease signifies arterio sclerosis of the coronary arteries This process occurs variously in different patients and displays multiple digressions that not only determine the resulting clin ical phenomena of the disease but also influence the pos sible response to therapeutic measures and therefore dictate their indication or contraindication The benefi cial effects of development of collateral circulation of the myocardium where single or multiple arterial tribu taries have become completely or partially occluded have been shown Thus a remarkably adequate myo cardial nutrition can be maintained the encompassing anastomosis acting as by pass in the region of arterial occlusions Sometimes new communications are quite ex tensive bridging the gap between main trunks and even resulting in new communications between branches of the right and left ventricles

Therapy must be individualized because routine treatment has undesirable consequences The first step is to limit the demands on the impaired heart by pro longed complete rest in bed or only moderate restriction *depending on severity of the disease* The patient should be encouraged to express his subjective feeling

(8) N w Y k St t J M d 4 409 41 M 1 1942

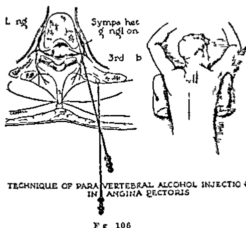
and about 1 to 2 oz clear pericardial fluid aspirated from the sac After exposure of the heart, a small healed infarct was seen on the anterior surface Branches of the left coronary artery were palpated and the anterior descending branch was found to be rigid and sclerotic The epicardium was caught by special long forceps near the origin of the great cardiac vein and the heart lifted forward slightly A flat rubber balloon cushion was introduced behind the heart to push it forward and rotate it to the right by gentle and slow inflation This maneuver was abandoned because it caused extrasystole with a pronounced drop in blood pressure and inability to feel the radial pulse A long gauze pack was introduced gently behind the heart to support it Dissection of the epicardium to expose the great cardiac vein just below the origin of the coronary sinus was a little troublesome because of fat and capillary oozing The vein when exposed was tied with a single ligature of no 2 white pleated silk The pericardium was left open to prevent pressure from reactionary pericardial fluid The pectoral muscle was sutured with interrupted catgut and the skin closed without drainage

Electrocardiograms made during operation showed remarkably little variation Immediately after operation the patient was placed in an oxygen tent and stayed there for several days During the first two postoperative days his course was uneventful without evidence of shock and a blood pressure of 100/70 Then pneumonia developed and cardiac arrhythmia suggestive of auricular fibrillation, but the pulse became regular Sulfapyridine brought the pneumonia under control Paroxysms of auricular fibrillation the longest lasting several hours continued to appear during the next week and then disappeared Further convalescence was uneventful

The patient has been seen at frequent intervals He is entirely free from pain and apparently well He does work he was unable to do before operation In February, 1940, he walked 5 miles without resting The electrocardiograms at present show no difference from those made three weeks after operation.

The authors recommend this operation only for patients with severe angina pectoris which has failed to respond adequately to medical treatment Until further experience is gained with venous ligation the operation should be regarded as a treatment for angina pectoris of atheromatous origin rather than for coronary disease as such There is of course no indication that ligation of the vein prevents thrombosis from occurring

of Horner's syndrome and elevation of skin temperature in the upper extremity of the side injected When these signs of nerve anesthetization appear 4 cc of 75 to 95 per cent alcohol is injected slowly through each needle and the needles are withdrawn The fluid remains between the pleura and the



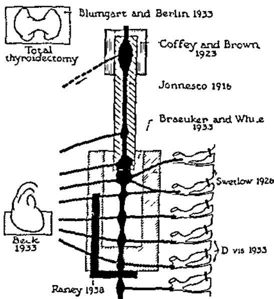
TECHNIQUE OF PARAVERTEBRAL ALCOHOL INJECTION IN ANGINA PECTORIS

Fig 106

intercostal membrane and bathes the ganglions and rami The degree of destruction of the ganglions and rami that results depends on accuracy of insertion of the needles.

Horner s syndrome develops in about 75 per cent of patients and remains for a long time in about 30 per cent Persistence of this sign indicates destruction of the stellate ganglion which is desirable but its absence does not always mean an improper injection because destruction of the rami only will also relieve cardiac pain

TECHNIC — A sedative is given to overcome apprehension. Injections are made on the side of severest pain but in cases of retrosternal pain, on the left side first. The patient is placed in prone position with the chest on a pillow and the neck flexed anteriorly (Fig 106). Landmarks for insertion of the *needles are the spinous processes*. A *long, fairly flexible* needle is inserted directly anteriorward through previously anesthetized skin about 3-4 cm from the midline opposite the seventh cervical to the fifth dorsal spines until it strikes the transverse process at a depth of 3 to 5 cm. At this point



SURGICAL MEASURES TO RELIEVE CARDIAC PAIN

Fig 105

1 cc of a 1 per cent procaine solution will prevent pain as the needle is forced over the inferior edge of the transverse process. It is then tilted about 20 degrees to the midline and inserted another 2 to 3 cm until the point touches the body of the vertebra. Frequent aspirations are necessary to avoid entering a blood vessel or the pleura or spinal canal. When all needles are in place, 2 cc of 2 per cent procaine solution is injected through each as a diagnostic test. If they are *placed properly* there will be complete anesthetization of the ganglions in 15 to 20 minutes as shown by development

ing for some board to establish certification of those physicians who are competent to interpret electrocardiograms thus to stop the present appalling practice of many wholly untrained and incompetent physicians who have purchased electrocardiographs and are using them daily in their offices with serene confidence in their ability to distinguish between the important and the unimportant changes in the curves

Fallacies in Application of Clinical Electrocardiography F A Willius states that about one third of the patients with coronary sclerosis accompanied by the anginal syndrome show no significant abnormalities in the electrocardiogram Physical examination of the heart may not disclose any evident alterations from the normal and the roentgenogram frequently shows a normal heart Here careful history taking will give the correct diagnosis In severe valvular disease with marked cardiac enlargement and even the existence of congestive heart failure the electrocardiogram may remain remarkably unaltered Under these circumstances the skilful utilization of the perceptive senses reveals the findings for correct diagnosis rather than use of mechanized methods of examination

In recent years the so called electrocardiographer has appeared He does not conform to the requisites of the physician and perilously exceeds the limitations of a good technician He learns the gross departures from the normal graph but does not learn the fundamental principles of the method its advantages and limitations under similar circumstances its range of normal and therefore finds himself in the throes of false optimism and faith The laboratory worker also has little or no interest or experience in clinical medicine and becomes intrigued by trivia and creates a formulary concept of interpretation Such a system appeals to the uninitiated owing to its superficial simplicity and apparent infallible comprehensiveness One system which Willius observed consisted of according an arbitrary percentage value to

( ) P St ff M t M y Cl 17 137 140 M 4 194

ELECTROCARDIOGRAPHY

Use and Abuse of the Electrocardiogram in Medical Practice H M Marvin[1] (Yale Univ) discusses the unquestionable value of electrocardiography in such conditions as irregularities of cardiac rhythm involvement of the heart during the course of systemic diseases acute myocardial infarction digitalis intoxication structural lesions and the various types of cardiac neuroses However its widespread use may actually be doing harm because of misunderstanding and ignorance of its limitations The changes in the ventricular complex, including its terminal portion are mainly responsible for the gross misuse of the method The average practitioner should realize that changes in this part of the curve have no specific significance with the exception of changes associated with myocardial infarction The electrocardiogram hardly ever gives any helpful information on the functional state of the heart muscle and thus the therapeutic question of the amount of rest and action and the quantity of digitalis to be given cannot be decided by the electrocardiogram Another misuse of the curves is to attempt to secure information about the prognosis from the electrocardiogram although it has been shown repeatedly that this is usually impossible The graphic records must be interpreted in the light of clinical evidence and in chronic heart disease it is the clinical picture and laboratory data which can be used as basis for estimating the prognosis Furthermore misinterpretation of the electrocardiogram is responsible for a large number of unjustified diagnoses of heart disease Such diagnosis should never be made because of some minor variation or change in the electrocardiogram alone in the absence of supporting clinical evidence This misuse is prevalent throughout the country The American Heart Association has received letters from leaders in the cardiovascular field everywhere ask

(1) New England J Med 6 13 17 Feb 5 1942

to determine whether any data of importance are contributed by the added effort and to consider whether such additional information justifies the increased cost and the heavier tax on the laboratory facilities and personnel Information was sought under the following three headings (1) the relation between increasing use of electrocardiography and the proportion of normal and abnormal records obtained (2) the clinical value of a representative group of electrocardiograms during a year of small demand as compared with a year of large demand (see table) (3) results of routine electrocardiograms taken on a large group of patients who would not otherwise have had the benefit of electrocardiographic study

EVALUATION OF ELECTROCARDIOGRAMS IN A YEAR OF SMALL DEMAND AND A YEAR OF LARGE DEMAND

	1934 100 ECG	1939 (100 ECG)
Class I (diagnostic)		
Group A—Unexpectedly normal	0	2
Group B—Unexpectedly abnormal	16	12
Total	16	14
Class II (helpful)		
Group A—Normal	5	7
Group B—Abnormal	34	40
Total	39	47
Class III (unhelpful)		
Group A—Normal	14	0
Group B—Abnormal	31	19
Total	45	39

Diagnostic [illegible]

The inquiry revealed that the proportion of abnormal records obtained has grown considerably and has practically paralleled the increasing demand the clinical value of a representative group of records in a year of high demand was fully as great as in an earlier year when records were requested only half as frequently (see table) Study of the results of routine electrocardiography showed a significant incidence of electro

various graphic abnormalities which in turn regardless of the presence or absence of heart disease was translated into clinical significance Such practice is dangerous and ridiculous Finally there is the individual who interests himself in electrocardiography purely from a remunerative standpoint No examination is complete in his opinion without an electrocardiographic examination His position is fortified by the laity who in their lack of understanding of this science request this examination with utmost belief One of the physician s many trusts is to deter the patient from unnecessary expenditures when he clearly realizes that a special diagnostic examination is not necessary The expression of a clinical opinion on part of an electrocardiographer who knows nothing of the patient s history or physical findings is utterly unwarranted and when rendered constitutes an absurdity which has regrettably become prevalent and is a destructive influence in clinical electrocardiography

Cardiologists and internists have the duty to correct this unfortunate situation This can be accomplished only by correct precept and example sound teaching and expression of audible disapproval when such instances come to their attention In most medical schools electrocardiography is offered as an elective course of which relatively few students avail themselves Possibly medical educators will view this problem in a different light and make electrocardiography a compulsory course and insist that it be taught in an interesting understanding and comprehensive manner

Justification for Increasing Use of Electrocardiography in Hospital Practice In face of the steadily increasing demand for a laboratory service in relation to the number of patients studied Arthur J Geiger Massimo Calabresi and Loren F Blaney[3] (Yale Univ) deemed it pertinent to inquire whether the augmented laboratory output is being accomplished at a relative loss in clinical value for each 100 electrocardiograms made

(3) Am J M Sc 03 219 31 Feb —

tion of the findings that constitute the characteristics of definitely abnormal electrocardiographic patterns

TABLE 1 —CLINICAL AND ELECTROCARDIOGRAPHIC CLASSIFICATION OF 229 CORPORATION EXECUTIVES

	Electrocardiographic Classification			
Clinical Classification	Normal	Questionable	Abnormal	Total
Normal	90	70	7	167
Questionable	8	15	0	23
Abnormal	8	22	9	39
Total	106	107	16	229

TABLE 2 —FOLLOW UP DATA IN THE GROUP OF 229 CORPORATION EXECUTIVES

	Electrocardiographic Classification			
Clinical Classification	Normal	Questionable	Abnormal	Total
Normal	5	8	5	18
Questionable	1	3	0	4
Abnormal	8	22	9	39
Total	14	33	14	61

This table is arranged like Table 1 and should be inspected with it. The figures in the various compartments of the table indicate the number of subjects [illegible] disease [illegible] such disease

cardiographic abnormalities beyond that which might be expected from other clinical evidence Thus the increasing use of electrocardiography in local hospital practice appears justified Requests for routine unnecessary electrocardiograms are decried, but their liberal use if applied judiciously and intelligently discloses abnormalities of clinical value sufficient to warrant the additional expenditure of laboratory service

Electrocardiography in Military Medicine Francis C Wood *Charles C Wolferth and T Grier Miller*[4] (Univ of Pennsylvania) made clinical and electrocardiographic surveys of various groups of college students who from the standpoint of age corresponded roughly to a group of army recruits and of 229 unselected corporation executives corresponding in age to a group of ... The following conclusions were reached

1 In ...rsons under 30 electrocardiographic study does not ...onstrate cardiac abnormalities of importance from ... military standpoint which are not discoverable on ...sical examination In the study of young persons ... heart disease is present or is suspected to be p... electrocardiography rarely adds further significant ...ormation Furthermore it may confuse the issue b... overing minor abnormalities in persons who have ... diac lesion of military significance

2 In persons over ... d especially in those over 40 electrocardiographic ... ay occasionally demonstrate degenerative heart dis... ile there are yet no physical signs or symptom... s existence In this age group the study of a ... th cardiac pain or with cardiac arrhythmia is ... lete without an electrocardiographic examinat... owever, even in the case of these older persons ... ctrocardiogram may confuse the issue oftener ... it clarifies it unless the examiner is aware of ... equent occurrence and relative insignificance ... questionable electrocardiographic abnormalit... unless he has a clear concep

and to the S T segment which occasionally became de pressed under the base line They appeared in a few hours after hemorrhage and disappeared in a few days They ap peared independent from the hemoglobin content of the blood and were found in patients without symptoms of shock Transfusions had no influence on them They may

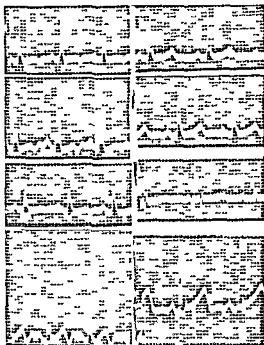


Fig 107 (left) —In t d T w nd d p f S T gm t l d I d II ft h m t m

Fig 108 (right) —S n day l t gm l l t d g m

be explained by the appearance of lesions in the myocar dium due to an insufficient blood supply to the heart this is a consequence of the circulatory adjustments fol lowing acute hemorrhage in which the coronary arteries participate One of the cases is given here

Negress 43 complained of vague gastric symptoms of sev

limits Q or S may be absent in one or more leads. S T segment iso electric

Category 3 —Normal variations P negative or absent, Q R or S splintered or notched, R less than 5 mm. in one or two leads T negative or diphasic in lead III, S T elevated or depressed auricular or ventricular extrasystoles

Category 4 —Doubtful abnormal Low voltage of R wave in all leads left or right axis deviation abnormal time relation hip of wave complexes, i e, prolonged P R prolonged QRS

Category 5 —Definitely abnormal T wave negative in lead I or II or both pathologic arrhythmias bundle branch block.

This arbitrary classification was required because of the scarcity of information of normal records for the age group (13 32) investigated The electrocardiograms of the first 2,000 air crew members were categorized as shown in the table Analysis of the table shows that the typical textbook electrocardiogram is rare Most records showed variations which necessitated categorization in group III The number of records showing axis deviation abnormalities of the T wave in leads I and II and the occurrence of prolonged P R and QRS intervals indicate the value of such recordings at least as an indication for more careful investigation before selection for air crew duties although it is fully recognized that the value of electrocardiography in diagnosing cardiac conditions is limited

ANALYSIS OF ELECTROCARDIOGRAMS OF 2 000 AIR CREW MEMBERS

CATEGORY	RECORDS	%
1	27	1 35
2	358	17 90
3	1,307	65 30
4	299	14 90
5	9	0 45

Electrocardiographic Changes Following Hematemesis in Peptic Ulcer David Scherf H Reinstein and S D Klotz[7] (New York Med College) report eight cases of peptic ulcer with alterations in the electrocardiogram following acute hematemesis The alterations were limited to the T wave, which became lower and inverted

(7) Rev G s e t r L 8 343 3 0 S it Oct

graphic changes during hyperpyrexia induced in the air conditioned cabinet of Kettering, through 52 treatments of 20 patients The changes were usually insignificant and quickly disappeared when the fever subsided In many cases a temporary overcompensation occurred in the late febrile or postfebrile period No permanent changes were noted In no instance in these patients all of whom had normal hearts were changes characteristic of coronary insufficiency observed and no cardiac damage appeared to have resulted as far as observation and clinical judgment could tell Apparently the changes are the result of physiologic processes incidental to the temperature increase without regard to the mode of its induction

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TREATMENT

Value of Physical Therapy in Management of the Cardiac Patient William C Leaman Jr[1] (Woman's Med College of Pennsylvania) states that the chronic sufferer from heart disease may believe that his problems are being inadequately cared for when the physician fails to use any of the physical therapeutic measures indicated for treatment of his type of cardiac disorder Consequently he turns from the physician with his knowledge of etiology pathology and treatment of heart disease to a member of a cult who usually knows little concerning the indications and contraindications of the various methods he uses Despite the limited training in physical therapy which the physician receives in medical school the physician should acquaint himself with the physical therapy measures available for treatment of cardiac conditions Spa treatment hydrotherapy exercise massage heliotherapy electrotherapy and occupational therapy are methods which under proper supervision and for carefully selected patients will produce beneficial results

(1) A h Phys Th py 23 5 13 J n ry 194

eral years duration She vomited coffee ground fluid for three days before admission and during the first day in the hospital Her stools were dark and tarry Her temperature was 100 F, pulse rate 120 and respirations 20 per minute The heart was of normal size and configuration, the sounds were of normal quality, and the blood pressure was 100/40 Gastro intestinal films taken after recovery from the acute phase of the illness showed a persistently irregular duodenal cap and fluoroscopy revealed a nichelike projection at the base of the cap Therapy consisted of the conventional diet for bleeding peptic ulcers transfusion was not given

At admission the hemoglobin was 30 per cent and the red cell count 1 300 000 Eight days later the hemoglobin was 40 per cent and the red cell count 2 060 000, 17 days after admission the hemoglobin and red cell count rose to 48 per cent and 2 390 000 respectively The first electrocardiogram (Fig 107) taken the second day of hospitalization showed inverted T waves in leads I and II without depression of the S T segments The T wave in the chest lead was diphasic with one part deeply inverted A second electrocardiogram (Fig 108) taken seven days later was normal

Electrocardiographic Study of the Effects of Boxing J Scott Butterworth and Charles A Poindexter[8] (Columbia Univ) took electrocardiograms of 35 young boxers before and after matches Following exercise there was a definite increase in the height of P_2 and P_3 and a decrease in the size of the T waves There is no evidence that boxing has any traumatic effect on the normal heart in this age group (16 24 years) The average values of the various deflections in the electrocardiograms corresponded fairly well with those in the literature for similar groups There were minor differences, due to position of subject emotional stress and similar factors *The diversity of the tracings in a group of normal persons* was of great interest It is recommended that anyone doing routine electrocardiographic interpretation study such a group carefully to refrain from reading too much into routine tracings.

***Electrocardiogram* in Induced Fever** Phillip T Knies[9] (Ohio State Univ) observed the electrocardio

(8) Am Heart J 3 59 63 June 1941 [...] ry 1942
(9) Ibid 2 804 810 December 1941

graphic changes during hyperpyrexia induced in the air conditioned cabinet of Kettering through 52 treatments of 20 patients The changes were usually insignificant and quickly disappeared when the fever subsided In many cases a temporary overcompensation occurred in the late febrile or postfebrile period No permanent changes were noted In no instance in these patients all of whom had normal hearts were changes characteristic of coronary insufficiency observed and no cardiac damage appeared to have resulted as far as observation and clinical judgment could tell Apparently the changes are the result of physiologic processes incidental to the temperature increase without regard to the mode of its induction

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TREATMENT

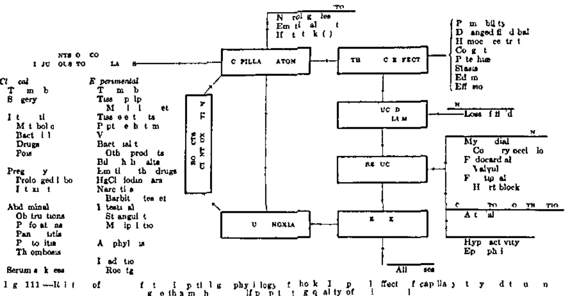
Value of Physical Therapy in Management of the Cardiac Patient William C Leaman Jr[1] (Woman s Med College of Pennsylvania) states that the chronic sufferer from heart disease may believe that his problems are being inadequately cared for when the physician fails to use any of the physical therapeutic measures indicated for treatment of his type of cardiac disorder Consequently he turns from the physician with his knowledge of etiology pathology and treatment of heart disease to a member of a cult who usually knows little concerning the indications and contraindications of the various methods he uses Despite the limited training in physical therapy which the physician receives in medical school the physician should acquaint himself with the physical therapy measures available for treatment of cardiac conditions Spa treatment hydrotherapy exercise massage heliotherapy electrotherapy and occupational therapy are methods which under proper supervision and for carefully selected patients will produce beneficial results

(1) A h Phy Th ry 3 5 13 J n ry 194

pears after injection If more than 50 cc fluid must be injected much time may be saved by using a manually operated two way stopcock with two thin walled rubber tubes one leading into the needle by an adapter and other leading into the reservoir holding the blood plasma or fluid to be injected (Fig 110) Then it becomes unnecessary to remove the syringe from the sternal needle every time it has to be filled If rapid rate of injection is required two needles may be inserted at once in the sternum one in the manubrium (above the angle of Louis) and the other 5 cm below it in the body of the sternum Since the marrow cavity of the manubrium and the body of the sternum seldom communicate the material will not come out of the other opening The two orifices must not be made in the same portion of the sternum unless the fluid is going in with the same pressure through both of them After injection the needle may be connected with a standard gravity infusion apparatus If the patient has reacted from collapse and the blood pressure has risen to normal, it may be possible to use peripheral veins

Vascular and Cellular Dynamics of Shock Virgil H Moon (Jefferson Med College) states that an analysis of the sources for disagreement concerning dynamics of shock indicates that four major causes have operated to confuse interpretations of its phenomena and of their interrelationships The first of these was deficient knowledge of capillary reactions and of circulatory disturbances originating in them A comprehension of these has contributed immeasurably to an understanding of shock resulting from trauma burns and other types of tissue damage Failure to distinguish between shock and hemorrhage has caused much confusion Hemorrhage is a potent contributory factor but the effects of uncomplicated hemorrhages present numerous features opposite in character from those which constitute the syndrome of shock Variations in blood pressure used as criterion and failure to consider the depressor effects of both anesthesia and losses of blood have led to undependable conclusions concerning the effects of absorption Experiments have shown that products derived from normal tissues, independent of narcosis and hemorrhage will produce the syndrome of sh

(5) Am J M Sc 203 1 18 Ja ary 1942


Drugs
Loss

by its characteristic features Hemoconcentration during life and presence of engorged capillaries stasis petechiae and edema after death indicate endothelial damage as a major factor The occurrence of these conditions in extensive visceral areas remote from the injury indicates systemic not local endothelial change and damage Shock, like other conditions of disease is accompanied by a pattern of morphologic changes which are related etiologically to its mechanism of origin and which corroborate the interpretation of shock as due to endothelial change Figure 111 presents an assembly of related facts concerning the picture of shock

Some Observations on Cardiovascular Changes in Shock Therapy Hervey Cleckley and DuBose Egleston Jr found that temporary arrhythmias and other electrocardiographic changes have been frequently recorded in the literature There is no conclusive evidence of permanent myocardial damage or other serious change in patients with normal cardiovascular systems at the beginning of treatment

The authors observed five cases in which alarming clinical signs immediately after convulsions were noted Definite electrocardiographic evidence of myocardial damage noted in one case 5 days after the last seizure had disappeared entirely 10 months later After seizures induced by metrazol cardiovascular reactions may occur which suggest dangerous effects Extreme or persistent cyanosis and dyspnea may indicate effects on the heart capable of producing significant pathologic changes Administration of atropine prior to metrazol therapy tends to prevent accumulation of excessive secretions in the air passages and diminishes dyspnea Administration of oxygen by intranasal catheter has also appeared to reduce these complications The authors believe that fatal cardiac disturbances or permanent myocardial damage is rare and that their occurrence should not discredit the use of metrazol in treatment of serious personality disorders

MISCELLANEOUS

Enlargement of the Heart Paul D White[6] (Harvard Univ) states that enlargement of the heart may be due to acute dilatation to preponderant hypertrophy or to both hypertrophy and dilatation of comparable degree It appears to start as an overstretching or dilatation of the myocardium work hypertrophy is largely a reaction of the heart muscle to injury and a failure of the myo cardium to return to its original size This stretching gradually increases until the heart becomes heavy al though often with relatively little dilatation of the chambers and the process accelerates to a state of clin ical myocardial insufficiency from which congestive heart failure results

Four conditions are occasionally responsible for a fairly acute dilatation of the heart two of which namely severe acute rheumatic myocarditis and excessive heart rate in paroxysmal tachycardia affect both ventricles the third acute massive myocardial infarction involves the left ventricle primarily and the fourth massive pul monary embolism involves the right ventricle (acute cor pulmonale) The acute dilatation may precipitate con gestive failure and death it may clear up almost or apparently completely on subsidence of the acute strain or it may as in many cases of acute rheumatic and acute coronary heart disease leave permanent enlargement of the heart consisting of both dilatation and secondary hypertrophy which may in chronic rheumatic heart be ascribed wrongly to coincident valvular deformity

Some hearts especially those under the strain of sys temic or pulmonary hypertension and of aortic stenosis show at first and for years preponderant hypertrophy dilating appreciably only at the time of final failure Others especially those with free aortic regurgitation show much dilatation at an early stage and also the highest degrees of hypertrophy The largest hearts in

(6) New E gl d J M d 5 571 574 Oct 9 1941

volume are those with mitral valve disease and auricular fibrillation in which the left auricle and often the right ventricle and right auricle become enormous, whereas the left ventricle is normal or actually small In most cases of cardiac enlargement the strain is left sided, from systemic hypertension aortic valve disease or myocardial infarction and the left ventricle consequently enlarges first and sometimes is the only heart chamber to do so Frequently it becomes incompetent and then in order first the left auricle next the right ventricle and finally the right auricle become enlarged It is enlargement of the left ventricle that increases the heart weight preponderantly that of the left auricle displaces the greatest space

Extracardiac factors such as anemia and myxedema may cause cardiac enlargement The strain may be largely acute and temporary and the enlargement may subside but it may also become permanent although this is more often due to intracardiac disease and systemic hypertension The prognosis of cardiac enlargement is summarized in the observation that the larger the heart the worse the future Treatment is directed to relief of the underlying strain as much as possible and the optional routine use of a daily ration of digitalis to help prevent or retard further cardiac enlargement and failure Administration of 1 to 1½ gr digitalis daily appears reasonable although the value of the drug has not been proved

Capacity of Coronary Bed in Cardiac Hypertrophy William Dock[7] (Stanford Univ) states that until diodrast clearance was used to study renal blood flow there was no yardstick of normal blood flow through human organs during life to compare with rates of flow observed during perfusion post mortem Use of the same technic on coronary arteries is described It was hoped to obtain information on the vascular bed of hypertrophied hearts to supplement that obtained by morphologic studies

After eliminating vascular rigor perfusing human hearts with kerosene under pressure post mortem gives values for coronary flow which seem an index of the maximum possible flow during life This is 3 1 cc per Gm per minute at 100 mm Hg in normal men under 40 It is 35 per cent lower in the hearts of those aged 60 80 and also falls in hypertrophied hearts In old people it is 30 per cent lower in hearts over 600 Gm than in those under 350 Gm In persons aged 40 60 it is 37 per cent lower in hearts over 600 Gm than in those under 350 Gm

There is no evidence that hypertrophied hearts have an inadequate oxygen supply or that their fibers are too thick for adequate oxygen diffusion Congestive fail ure cannot be ascribed to anoxia except in the presence of severe anemia coronary occlusion or tachycardia with low blood pressure Decrease in perfusibility with age and growth may be a perfectly normal adaptation of the needs of the tissue the perfusibility of the heart of the young adult is about half that of an infant at 2 years The thesis can be accepted that the hypertrophied heart has a vascular bed ample for its needs and that its fibers can be fully supplied with oxygen There need be no insistence that the growth of the vascular bed exactly parallels an organ s increase in bulk The pathologist may even be pleased that he need not explain to students why anoxia of heart muscle due to severe anemia or to coronary occlusion causes fatty degeneration while the alleged anoxia of hypertrophy rarely does Those who ascribe angina to myocardial ischemia will not find it easier to explain why angina is far less frequent with simple hypertrophy than with anemia and coronary dis ease This may compensate for losing an explanation of myocardial failure which raised more questions than it answered

Cardiovascular Examination of the Army Recruit Henry Jackson Jr [9] (Boston City Hosp) discusses the mobilization regulations To be accepted in class 1A a

(9) New E gl 1 J M d 25 99 998 D 1941

recruit must have a cardiovascular apparatus free from all but the most trivial deviations from the strict normal The apex impulse must be within the midclavicular line and no thrills or important murmurs may be present Pulse rate must be under 100 and over 50 No cardiac arrhythmias are allowed other than sinus arrhythmia and extrasystoles More than transitory hypertension patently due to excitement is disqualifying Neurocirculatory asthenia unless mild is a cause of rejection The induction centers, in contrast to local examining boards either flatly accept or reject a man The Army does not now consider class 1B except under special circumstances requiring a waiver from the War Department Thus the induction centers differ from the local examining and advisory boards which may at their discretion place a man in class 1A, 1B or 4

According to the same regulations it is incumbent on examining physicians to accept for service men with accidental functional murmurs or with other findings that do not indicate disease or impair the selectee s ability to undergo severe bodily exertion and to exclude those with defects however innocent appearing at examination that would interfere with their activities Certain conclusions based on experience at the Boston Induction Center Fourth Recruiting Area and on help given by several cardiovascular experts, are presented

All recruits with organic heart disease of whatever nature should be rejected Men with a diastolic murmur at the apex or base and with undoubted history of rheumatic fever and those showing arteriosclerosis or arteriolar sclerosis or any gross inequality of the pulse should be rejected A mitral systolic murmur accompanied by an increased pulmonic second sound slight cardiac enlargement and history of rheumatic fever is cause for rejection It is wise to reject any man with a loud harsh systolic murmur transmitted to the axilla even though it is unaccompanied by other pathologic signs The true presystolic murmur is also cause for rejection Men with pulse rates of 100 or over should be rejected unless

tachycardia subsides with adequate rest. Men whose systolic blood pressures remain over 150 and whose diastolic pressures remain over 90 during the day of examination are rejected. Tables 1 and 2 present the causes *of rejection for cardiovascular defects*. The reason for the difference in the number and percentage of rejections is that an increasing belief on the part of the examiners exists that the standards for acceptance (class 1A) must be of the strictest sort.

TABLE 1.—REJECTIONS DUE TO CARDIOVASCULAR ABNORMALITIES IN 1940 (8 708 MEN)

Cause of Rejection		No. Rejected
Essential hypertension		39
Rheumatic heart disease		15
Mitral stenosis	4	
Aortic regurgitation	2	
Mitral regurgitation	1	
Unspecified	8	
Neurocirculatory asthenia		6
Organic heart disease, type unspecified		4
Tachycardia		4
Hypertensive heart disease		1
Auricular fibrillation		1
Total rejections for cardiovascular disease		70
Percentage of total examinations		0.8
Percentage of total rejections		4.9

TABLE 2.—REJECTIONS DUE TO CARDIOVASCULAR ABNORMALITIES IN 1941 (8 627 MEN)

Cause of Rejection		No. Rejected
Essential hypertension		88
Rheumatic heart disease		39
Mitral disease	14	
Aortic disease	2	
Mitral and aortic disease	1	
Unspecified	22	
Neurocirculatory asthenia		36
Organic heart disease, type unspecified		10
Tachycardia		8
Congenital heart disease		2
Auricular fibrillation		1
Paroxysmal tachycardia		1
Multiple extrasystoles		1
Total rejections for cardiovascular disease		186
Percentage of total examinations		2.1
Percentage of total rejections		13.3

Evaluation of Heart Signs in Navy Recruiting Elmer F Lowry[1] (M C USN) points out that irregularities of heart action may frequently be present without heart disease and that great damage may be done by labeling such conditions heart disease The excitement usually exhibited by young Navy recruits may cause abnormalities and irregularities in heart beat and sound which will disappear later In a recruit with a well developed body and strong virile physical and mental reactions heart disease is not likely to be found even in the presence of some of the classic signs such as murmurs tachycardia and hypertension On the other hand in any individual with poor physical or mental development classic signs and symptoms assume serious significance A high rate of poor teeth has been observed associated with heart irregularities and general underdevelopment and frequently a history of rheumatic disease Lowry discusses some of the signs of heart disease as they pertain to the selection of men for enlistment in the Navy

Tachycardia—This may be caused by excitement during examination at the recruiting office and abnormal stimulation of the sympathetic nervous system by the sensation of air on the undressed body Experience has shown that the pulse rate is much less when the applicant is completely dressed It apparently has no relation to heart disease in most cases and may disappear in a few minutes on resting It should not be considered indicative of heart disease until a thorough investigation of the man has actually shown heart disease to be present

Bradycardia—Navy physical standard requirement is that the pulse rate be at least 50 per minute under 50 is cause for rejection Lowry has never found a pulse rate as low as 50 in an applicant If the rate is below 50 serious heart disease should be assumed

Alterations in Size and Location of the Heart—It is difficult to find slight enlargement or slight dislocations

(1) Mil Surgeon 90 37 44 January 1942

of the heart by the physical examinations given at a recruiting station Alterations in size which can be observed during routine examination do not often occur in young men presenting themselves for enlistment Such enlargement would indicate grave disease which would probably manifest itself by unmistakable symptoms In most such cases the men are quite ill and would not enlist

Dislocations of the heart without apparent symptoms have occasionally been observed Dextrocardia is possibly the most frequent which can be detected It should be readily found if the heart is well to the right of the sternum and percussion along there will usually reveal it Absence of the apex impulse from its usual location should be a danger signal Although dextrocardia in itself probably produces no disability in many cases it is a form of congenital malformation and apparently indicates a lack of stamina in many cases and consequently a fertile field for more active and disabling cardiac infections If the applicant is well developed physically mentally sound and has no cyanosis and other symptoms of inadequate heart function dextrocardia should not be a cause of rejection and the man should be given an opportunity to serve

Hypertension—The lower limit of acceptable blood pressure is 100 mg Hg and the upper limit 140 systolic Persistent blood pressure outside of these limits is cause for rejection The man s general appearance his posture color strength and endurance and past medical history should determine acceptance if the blood pressure is *abnormal Past medical history is most* important because some men develop into remarkably fine looking and intelligent specimens despite heart disease and frequently all physical signs are absent when disease is known to be present only the history in such cases may lead to a sufficiently thorough search to detect the disease

Murmurs—Blowing murmurs at the apex transmitted to the left and even to the axilla as well as in numerous

other areas around the precordium are frequently found during examination of excited young men Sometimes these murmurs are systolic in time and sometimes diastolic and are accompanied by rumbles and thrills frequently heard in mitral stenosis This should not be labeled valvular disease only occasionally does this indicate or develop into cardiovascular disease Serious cardiovascular disease is probably always accompanied by illness lack of normal endurance, cyanosis or poor posture history of rheumatic fever or chorea or something else which will give a definite clue

Arrhythmias—This is found quite often in examining recruits The most frequent form is alternation of fast and slow beats similar in rhythm to that of heart block, and is found in numerous conditions which are apparently not abnormal In absence of cardiac symptoms it has little or no prognostic significance according to Bishop

Cardiovascular Aspects of Aviation Medicine John R Poppen[2] (M C U S N) states that flying personnel must be free from organic disease particularly of the cardiovascular system because of the unusual strain to which it is subjected in flying Flying requires adjustment to a new and unusual set of circumstances in its three dimensional fields With rapid changes in altitude come problems of anoxia and high accelerations. The profound changes in blood distribution incident to the centrifugal forces encountered in certain maneuvers place a peculiar burden on the circulation in which the heart has its share The responsibility of repeatedly and suddenly requiring an effort to preserve the circulation against profound reduction and inadequate filling of the right heart is peculiar to flying These are unhuman circumstances and not reasonable tasks to present to a heart unless it is free from actual or incipient organic inefficiency

Diagnostic methods for determination of actual or incipient organic heart disease include careful history

(2) New England J Med 5 892 896 Dec 4, 19

keen inspection accurate percussion and clear ausculta tion supplemented by electrocardiographic and roent genographic examinations It is unfortunate that more apparatus and more trained personnel are not available for the reading of electrocardiograms at the various training centers

The cardiovascular problem of maintaining flying fitness is largely that of avoiding the development of what has been variously named but fairly uniformly defined as neurocirculatory asthenia effort syn drome ' soldier s heart ' Poppen prefers the term staleness because it avoids implication that the condi tion is exclusively a circulatory disturbance particular ly in its etiology To avoid or relieve the condition it must be discovered in its earliest and most incipient stages The Schneider index has been used in circulatory efficiency rating for some years Six factors—reclining pulse rate standing pulse rate increase in pulse rate from reclining to standing increase in pulse rate fol lowing standard exercise time of return to standing rate and change in systolic blood pressure from reclin ing to standing—are scored on the basis that each is capable of a score of 3 The six are added giving a total score or index Much criticism has lately been leveled against the Schneider index but it continues to have the advantages of giving valuable information if prop erly interpreted requiring minimum equipment and comparatively untrained assistants Furthermore it has acquired a meaning to the pilots and thus has psychologic value

Effects of Physical Strain and High Altitudes on Heart and Circulation D B Dill[3] (Harvard Univ) discusses recent observations regarding the dependence of cardiovascular responses to moderate and severe ex ercise and high altitudes on age training race and environmental conditions Measures of cardiovascular function used include the heart rate total oxygen uptake a derived function oxygen pulse and cardiac

output Total oxygen intake during maximal work is perhaps the best functional test of cardiorespiratory performance It depends on volume of air supplied to the lungs conditions controlling diffusion in the lungs the rate of blood flow and the oxygen content and carrying capacity of venous blood The "oxygen pulse" is derived from the first two functions, it amounts to the oxygen delivered to the tissues per beat of the heart Cardiac output in man is best measured by the acetylene method of Grollman

Cardiovascular responses to moderate exercise have a notable dependence on age The performance of a number of persons doing a fixed task on the treadmill, i e walking at 5 6 kilometers per hour up a grade of 8 6 per cent was studied Oxygen consumption was about seven times the basal rate The heart rate after 15 minutes of such work is much higher in boys than in men of middle age Robinson showed that such work produces a mean heart rate of 170 in 6 year old boys as contrasted with 134 in men of 42 (Table 1)

TABLE 1 – HEART RATES DURING GRADE WALKING

(Speed was 5 6 km per hour and grade 8 6 per cent This raises oxygen consumption to about seven times basal)

AGE YR	HEART RATE
6	1[illegible]0
10	164
14	160
18	1[illegible]0
22	146
26	143
30	140
34	137
38	131
42	134

Quantitative measurements of the capacity for work of the body as a whole reveal that man's best performance during intense activity is attained between 18 and 2[illegible] years His maximum heart rate then lies between 190 and 210, and he can reach higher levels of oxygen consumption during this time than ever again Thereafter his decline can be traced (H[illegible] [illegible]able

to use 4 L oxygen per minute at 20 and only 3 L per minute at 50 years At the same time the maximum heart rate he can attain during exercise falls off it is likely to lie between 160 and 170 at 50 years and may not exceed 150 at 70 years Since 1928 Dill's own maximum heart rate has declined from 172 to 162 per minute and his maximum oxygen consumption from about 3 3 L to 2 9 L per minute (Table 2)

TABLE 2—MAXIMAL ATTAINABLE OXYGEN INTAKE OF THE AUTHOR FROM AGE 37 TO 50

YEAR	MAXIMAL OXYGEN INTAKE (L PER MIN)
1928	3 28
1930	3 26
1931	3 35
1933	3 23
1935	3 [illegible]6
1936	3 17
1937	2 90
1939	2 98
1941	2 87

Aeroembolism experienced at 30 000 ft altitude and likely to occur after some time at 40 000 ft altitude is one of the most serious problems of the present era of military aviation Aeroembolism may always be attributed to the formation of gas bubbles in tissues or body fluids The formation of these bubbles has a simple physical explanation—a sudden reduction in pressure to one fifth atmospheric produces a supersaturated solution of nitrogen four fifths of this nitrogen is in an unstable state Much of it is eliminated by the lungs but some bubbles form in the tissues Once a bubble forms it may grow by accretion Both carbon dioxide and oxygen diffuse into it so that gas collected from emboli may contain no more than 50 per cent nitrogen Symptoms that may be caused by aeroembolism are bends (particularly the knee and ankle) itching (technically known as *formication*) *second degree formication* (itching merging into pain) throat irritation and headache There is no known remedy for aeroembolism Much can be done in the way of selecting resistant per

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sons The preliminary breathing of oxygen while exercising greatly increases tolerance but this is not practical in many situations

Dyspnea in Heart Disease R L Parker[4] discusses the pathologic physiology of dyspnea and several of the common associated clinical problems which are difficult to interpret Functional dyspnea frequently present in the nervously exhausted patient especially one with cardiac anxiety, must be differentiated from dyspnea of cardiac origin The dyspnea of which these patients complain is described as a sensation of weight in the thorax and inability to obtain a deep breath. Voluntary effort to overcome this sensation leads to periodic sighing and frequently the patient will demonstrate this type of sighing respiration during examination With severe emotional strain hyperpnea may develop to the extent that hyperventilation tetany or syncope may result The consciousness of respiratory difficulty of these patients invariably is precipitated by nervous and emotional strain rather than by physical activity

Evaluation of the cardiac status of the patient with chronic asthmatic bronchitis may be difficult As a general rule, patients who have not reached middle age and have no positive indications or organic cardiac disease should be treated for asthma alone However, for patients who have passed middle age and do not have a preceding history of asthma and whose asthma did not follow directly an infection of the upper respiratory tract the heart should be considered the offending organ until proved otherwise In most cases onset of cardiac asthma is preceded by gradually increasing dyspnea on exertion Determination of circulation time with decholin and determination of venous pressure will give additional important information of the cardiac status A delay of 18 seconds or more in circulation time and a venous pressure above 80 mm water indicate associated cardiac failure The reaction to mercurial diuretics is informative If cardiac failure is present in

(4) P c Staff Me t M y Cl[illegible]

travenous injection of one of the mercurial diuretics usually provokes diuresis of 2 500 cc or more of urine in 24 hours with appreciable improvement in respiration If cardiac failure is not present despite the asthma *little or no beneficial effect on respiration* will be *noted* and the diuretic response will be much less marked

Dyspnea associated with pulmonary emphysema or diffuse pulmonary fibrosis may be differentiated in most cases because the dyspnea will have been present for years, whereas dyspnea of cardiac origin usually indicates a more rapidly progressive lesion

The obese patient usually complains of shortness of breath If the degree of dyspnea present is merely the reflection of a progressive gain in weight and there is no positive indication of cardiac disease there should be no serious cause for alarm If however in the absence of progressive weight gain the obese patient finds himself dyspneic under activities recently undertaken with ease the possibility of cardiac disease becomes more serious Reduction of weight in either case is the most important therapeutic procedure When obesity adds *materially to the burden of the heart the improvement* obtained by reduction of weight is often amazing

Myocardial Degeneration with Hypertrophy and Failure of Unknown Cause John A Reisinger and Basil Blumenthal[6] (Veterans Administration Washington D C) confirm the concept that myocardial insufficiency occurs without valvular deformity or hypertension even when there are causes for strain failure may be primarily due to depression of myocardial function by intoxications infections or metabolic disorders Frequently inadequate coronary blood supply caused by coronary arteriosclerosis is responsible for the myocardial damage although the possible noxious agents are numerous In middle aged and older adults coronary arteriosclerosis is often considered the etiologic agent for myocardial insufficiency such reasoning may give the correct diagnosis but there is danger of abuse

(6) Am. H rt J 811 8 4, D emb 1941

of the etiologic classification of coronary arteriosclerosis. The possibility that cardiac enlargement and myocardial insufficiency may occur without more common causes and actually without discoverable cause should be emphasized. Five cases are presented in which degenerative changes in the myocardium had no apparent cause. All had cardiac hypertrophy and myocardial degeneration without evidence of hypertension, valvular disease or coronary artery disease. None had hyperthyroidism, severe anemia, metabolic disorders or avitaminosis, and autopsy examination revealed no definite etiologic clues.

Four of the five presented suggestive evidence of syphilis in the history, serologic reaction or aorta which did not affect the coronary ostiums or aortic valve enough to account for the myocardial damage. One patient, a Negro, had no history of infection, treatment or positive serologic reaction, although the spinal fluid was not examined; the aorta was not grossly involved and therefore no definite evidence of syphilis was found. However, the possibility that syphilis was responsible for the cardiac manifestation in the other four cannot be dismissed, even though there is no proof that Spirochaeta pallida can attack the myocardium directly (except in producing gummous lesions).

Pulmonary Infarction in Heart Disease. Laurence E. Hines and Jordan T. Hunt[7] (Northwestern Univ.) report a survey of 1,311 autopsy cases over six years, of which 101 had gross pulmonary infarction. Heart disease, the principal cause of death in 234 cases, was accompanied by gross pulmonary infarction 81 times; clinical diagnosis of pulmonary infarction was made only twice. This striking diagnostic failure prompted an analysis of the clinical symptoms and signs presented by these patients. As controls, patients with heart disease without infarction were similarly analyzed. The results, compared in Tables 1, 2 and 3, explain the high incidence of diagnostic failure, since symptoms consid-

(7) Ann. Int. Med. 15: 644-64, October 1941.

ered characteristic of pulmonary infarction can also be explained as symptoms of heart failure Patients with symptoms of hemoptysis pleural pain cough dyspnea cyanosis fever percussion dulness or pulmonary rales have received diagnosis of heart failure rather than pulmonary infarct Analysis reveals only minor differences with the exception of hemoptysis which occurs in 35 per cent of patients with infarction and in only 8 per cent of the others Observations on a small number of patients point to persistent recurrent hemoptysis as a distinctive feature of the disease

Table 2 shows the incidence of pulmonary infarction in the various etiologic types of heart disease although a higher incidence is present in bacterial endocarditis there is no essential difference in the rheumatic vascular or syphilitic groups

TABLE 1—AUTOPSY INCIDENCE OF PULMONARY INFARCTION (1931–1933)

No of autopsies reviewed	1 311
Patients dying of heart disease	234
No of patients with pulmonary infarction	101
Cause of infarction Heart disease	81
Noncardiac	20
Clinical diagnosis of infarction (heart cases)	2

TABLE 2—AUTOPSY INCIDENCE OF PULMONARY INFARCTION IN ETIOLOGIC TYPES OF HEART DISEASE

	Cases	Incidence Infarct	Incidence %
Hypertensive or arteriosclerosis	161	48	30
Rheumatic type	33	12	6
Syphilitic	15	5	33
Bacterial	16	10	62
Congenital	1	0	0
Combined syphilis and arteriosclerosis	7	5	71
Combined rheumatic and arteriosclerosis	1	1	100

[illegible]

Emboli large enough to occlude the pulmonary artery or main branches cause a symptom complex character

ized by hemoptysis, marked dyspnea, cyanosis, substernal oppression and peripheral circulatory collapse (weak pulse profuse sweating ashen pallor, lowered blood pressure) This picture is generally distinctive enough even if heart disease is present, to lead to correct diagnosis Moderate sized emboli however, produce a picture which is inadequate for diagnosis in patients with heart failure As aid in this diagnostic dilemma, the authors suggest that the high incidence of pulmonary infarction be kept in mind when treating patients with heart disease infarction of the lung should be considered when the patient has persistent or recurrent hemoptysis persistent deep cyanosis unexplained jaundice or fever or sudden onset of heart failure not explained by overexertion or infection Finally, critical analysis of roentgen films of proved cases may lead to establishment of typical roentgen findings for this condition

TABLE 3 —Comparative Frequency of Physical Findings with Pulmonary Infarction

	Total Cases	With Finding	% Incidence of Finding	Total Cases	With Finding	% Incidence of Finding
Cyanosis	81	48	62	161	80	50
F[illegible]	81	39†	48	161	52‡	33
Signs of pulmonary consolidation	81	21	25	161	30	19
Signs of congestive heart failure	81	71	87	161	154	94
Auricular fibrillation	81	29	36	161	53	35

No [illegible] data o[illegible] fr[illegible]tion [illegible]ub
† Eight of this group had pn[illegible]m[illegible]n
‡ Twenty [illegible] of this gr[illegible]p had pa[illegible]um[illegible]nia

Dissecting Aneurysm of the Aorta Clayton D Mote and Jesse L Carr[8] (San Francisco) present 64 cases of dissecting aneurysm This condition occurs primarily in arteriosclerosis and exceptionally in syphilis or a combination of these In this series, syphilis was found without atherosclerosis in only two patients

According to Shennan, the immediate or exciting

(8) Am Hea t J 4 69 87 July 194

cause is a sudden increase of blood pressure due to physical or mental strains and stresses The point of initiation is a ruptured vasa vasorum in a weakened media which forms a small spreading hematoma The process usually occurs without demonstrable pathologic changes in the vasa vasorum but rather as a disease of the aortic media only In rare cases the point of initiation is a tear in the intima at the site of atherotic deposits usually the location of the tear in the intima bears no relation to disease of the intima but rather depends on underlying medial changes in the elastic lamina and on the dynamics of the aortic pulsations The dissection may remain static it may however rupture either through the adventitia with hemorrhage into the adjacent structures especially the pericardial cavity or back into the aortic lumen Elliotson stated that the occurrence of a rupture was not necessarily dependent on elevation in blood pressure but that it could be adequately explained on the basis of the degenerative lesion of the media In the authors series blood pressure was elevated in 7 and normal in 19 In one case blood pressure was normal a few hours before onset of dissection and on many subsequent occasions the systolic pressure was always the same This appears to support the suggestion that elevated blood pressure is not essential for formation of dissecting aneurysm

Dissecting aneurysm of the aorta is not as rare as hospital records indicate Owing to its rapid and fulminating character it frequently results in sudden death precluding hospitalization External trauma is not a predisposing factor to production of a dissecting aneurysm Antemortem diagnosis of the condition is made with increasing frequency and will be made even more often if the not uncommon occurrence of the disease is remembered and its characteristic findings are brought out by careful clinical observation

Clinical Method for Determining Blood Velocity in the Venous System is described by C Grill[9] Venous

(9) A t m d S d 108 1 39 1941

pressure in the cubital fossa is determined by means of a phlebomanometer. The cuff of a blood pressure apparatus is inflated to 60 mm Hg and the time required for the venous pressure to rise from 10 to 40 cm water is determined. The speed of this rise is a relative measure for blood velocity in the veins of the forearm. Average time in normal subjects was 41 seconds for males and 33 seconds for females. Considerable daily variations are noted in the same individual, and basal conditions of complete rest and fasting are desirable to obtain basis figures. The speed of rise is directly proportionate to the heart rate. Measurements in hemiplegic patients showed a slower rise of venous pressure in the paretic arm. Pressure rises more rapidly than normal in patients with anemia, thyrotoxicosis, fever and hypertension, while marked slowing was noted in a patient with Addison's disease and one with thrombo-angiitis obliterans. In patients with myocardial disease and valvular lesions the rise in pressure was slower than expected for the heart rate.

Disturbances in Cardiac Rhythm Following Roentgen Irradiation. P. Eggers[1] observed four patients aged 52, 53, 54 and 65 with cancer of the lung, and one aged 68 had metastasis to the lungs from gastric cancer. All received irradiation of the chest. In a patient, aged 38, with myeloic leukemia the spleen was irradiated. The one patient with gastric cancer also had metastatic lesions in the pericardium; the others were thought to be free from heart disease.

Transient auricular fibrillation was noted in three instances; in one of these there was alternation with premature auricular beats, and in another premature ventricular beats were superimposed on auricular fibrillation. In two instances auricular fibrillation became permanent during a relatively short period of observation. One patient showed transient appearance of premature beats of varying origin. An increase in voltage of the T deflections was noted following discontinuation

(1) Münch [illegible] Wchnschr 88 4 44 Feb 8

of roentgen treatment Both direct and indirect effects of the radiation on the heart are discussed by Eggers

Quantitative Changes of Residual Blood of the Heart with Physiologic and Pathologic Conditions O Agren states that physiologic and pathologic changes in cardiac volume occur more frequently than is realized and evidently imply important variations in the amount of residual blood The method consisted of taking simultaneous anterior and lateral teleroentgenograms and mathematically calculating the heart volume Normally the heart volume increases on the average 269 cc when a change is made from the erect to the recumbent position Work on a bicycle ergograph showed an increase in volume of 110 cc and after work a decrease to a *volume slightly below the initial volume*

Of the many studies made the following cases are illustrative (1) In a patient suffering severe attacks of bronchial asthma on a day free from attack the heart volumes during inspiration and expiration were 510 and 520 cc respectively During the attacks the figures were 650 and 530 cc this difference was far less noticeable after the attack had been abolished by adrenalin (2) An elderly man with coronary artery sclerosis and dyspnea for two to three years showed pulmonary congestion but no other evidence of congestive failure He lost 6 6 lb *in a week during which the residual blood* decreased by 330 cc (3) An elderly woman with hypertension was fully compensated at rest She was kept in bed and received small amounts of digitalis Within two weeks systolic blood pressure dropped from 250 to 175 mm Hg and residual blood decreased by 180 cc (4) A patient with paroxysmal tachycardia showed in two days an increase of 150 cc A week later after the attack had receded the residual blood had decreased by 200 cc (5) In a patient with beriberi heart in grave cardiac and renal failure quick recovery resulted following administration of vitamin B_1 The volume of residual blood decreased by 2J0 cc in 28 days

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Capillary Studies in Raynaud's Disease Felix Deutsch Otto Ehrentheil and Octavia Peirson[3] (Massachusetts Gen l Hosp) report an investigation of the constitutional capillary disturbances the functional processes in the capillaries and the capillary permeability in cases of Raynaud's disease These factors were studied both before and after preganglionic sympathectomy

Capillaroscopic observations showed that the disease may be present before the appearance of clinical symptoms In such cases abnormal capillaries can be seen when other vasomotor symptoms are not present. In most cases there was persistence of the subpapillary plexus and a persistent connection between it and the outgrowing capillaries Two objective measurements are introduced to test the dynamics of capillary circulation (1) *reflux time* i e that time which elapses *before the capillary* flow ceases, when the upper arm *is compressed with* a blood pressure cuff pumped up to

icallv but retain their subjective complaints because a neurosis may become apparent which may have been a part of the picture from the beginning

Peripheral Arteriosclerosis Nathaniel C Schlossmann and Leon Gerber[4] (Mount Sinai Hosp New York City) studied the vascular tree in 74 cases of gangrene of the lower leg necessitating amputation to establish the pathogenic events leading to occlusion and to classify the types of arterial occlusion The role of mural hemorrhage was emphasized as the most frequent



Fig 112 (left) —I t t th m to s ab t m l hyp rpl t pl qu w th mall p iet l lyi g th mb × 17
Fig 113 (right) —S m l t lev l f ul t t l m w th p ag f bl od l m nts t b d th l l p t f pl q × 15

factor precipitating acute luminal thrombosis A study of the atheroma its capillarization and the state of its stroma was reviewed to establish the fact that intimal hemorrhage was secondary to rhexis of the vascular channels traversing the necrotic atheroma All types of occluding mechanisms were considered to determine the importance of each as shown in the table Arteriosclerosis with severe encroachment of the lumen was second in frequency to thrombosis on atherohematoma Intimal and medial capillarization in arteriosclerotic

(4) An S g 115 292 307 F brn ry 1942

vessels could be traced to both the lumen and the vasa vasorum No difference was noted between the arteriosclerotic findings in the diabetic and the nondiabetic specimens studied

MECHANISMS OF PERIPHERAL VASCULAR OCCLUSION

GROUP			NO OF SPECIMENS	%
I		Thrombosis secondary to hemorrhage	36	49
II		Thrombosis on a plaque	5	7
III		Massive hematoma of the wall	1	1
IV	1	Arteriosclerosis with severe luminal encroachment	11	15
	2	Arteriosclerosis with narrowing and thrombosis	1	1
	3	Arteriosclerosis with mural hemorrhage	4	5
	4	Arteriosclerosis with hemorrhage and thrombosis	1	1
V		Granulation tissue	15	20
		Total number of specimens	74	

Arterial Occlusion in Relation to Effort Howard B Sprague and Walter Westinghouse[5] (Massachusetts Gen l Hosp) studied 75 attacks of acute arterial occlusion in 75 ambulatory patients 30 occurred in the retinal arteries of 29 of the patients and 47 occurred in other peripheral arteries of 46 In three cases occlusion took place during rather severe effort and in two a few minutes after unusual exertion in 37 it occurred coincident with mild or moderate effort and in 35 when the patient was at rest in bed or a chair

Peripheral arterial occlusion from embolism thrombosis or endarteritis rarely occurs during unusual physical effort even in patient with cardiovascular disease of a degree compatible with quite strenuous exertion In this series such occlusion occurred about 14 times as commonly when the patient was at complete rest or when engaged in the ordinary exertions of his usual life In about half the series of arterial occlusion—embolic and obliterative—the patient was physically inactive This suggests that the conditions necessary for either embolism or thrombosis are as effective with reduced as with increased blood flow and that the occurrence of such an accident is at least fortuitous

(5) New E gl d J Med 2 100 1008 De

Intermittent Claudication as Result of Arterial Spasm Induced by Walking William V Leary and Edgar V Allen[6] (Mayo Clinic) report on four patients whose distress was caused by diminished blood flow to the extremities the diminution of blood flow definitely resulted from spasm of the arteries but why this spasm occurred cannot be explained for the usual arterial response to exercise is arterial dilatation. One case is given here

Man 44 in 1935 complained of epigastric distress sugges tive of ulcer and muscular exhaustion in the entire left leg precipitated by strenuous walking and relieved by resting Because of normal pulsation of the leg arteries and mild ne s of the symptoms nothing further was done until 1939 when he complained of weakne s of both legs and trunk caudad to the level of the third lumbar vertebra present only after walking and disappearing after rest

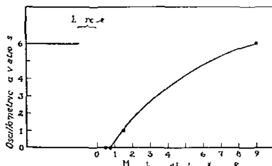


Fig 114.—C e I O ll met d t n t ken b kl f unt bef d t rm l t l pulsat d mpl te ab e f ill t mm d t ly ft r nd t b f rt l pul t Puls t h w er gr d lly tu d t n rm l ght m ut ft t f se

Pulsations of the dorsalis pedis and posterior tibial arteries were normal when at rest but after exercise the pulsations in the e arteries disappeared entirely and reappeared about a minute after cessation of exercise When the patient was at rest a systolic murmur was audible over the lower portion of the abdomen its maximal intensity was at the midline just below the umbilicus and its maximal transmission was to the femoral arteries After exercise a thrill was palpable over

(6) Am. H rt J 719- 25 D mb 1941

The two obliterative vascular diseases commonly seen are Buerger's disease and peripheral arteriosclerosis. Though the pathologic changes are profoundly different in the two diseases, the result in each is an intermittently progressive slowing of the circulation which manifests itself by a distinctive clinical picture. In many cases of either disease there is an associated degree of vasospasm which contributes materially to the diminished blood flow. The degree of this vasospasm can be measured by preoperative tests such as the spinal anesthesia and the Landis test. Harris believes that the spinal anesthesia test is the more informative. The Landis test is dependent on reflex dilatation of peripheral vessels when the hands are dipped in hot water. Spinal anesthesia paralyzes the outflow of sympathetic fibers. It most closely reproduces the effect which will be produced by lumbar sympathectomy. It often demonstrates some degree of vasospasm when the Landis test shows none. Both tests depend on measurements of skin temperature under controlled conditions. A rise in skin temperature indicates increase in blood flow resulting from the release of vasospasm.

If preoperative tests show that the skin temperature of the foot rises 3 C., a good result from lumbar sympathectomy can be predicted. There are many cases in which this test is negative and in which sympathectomy may be indicated. Even if the rest pain only is relieved, the result may be worth while if amputation is avoided or postponed for some years. Harris uses lumbar sympathectomy in all severe cases. If sympathectomy is to be used, it should be performed before gangrene and open trophic lesions have developed.

During the past 10 years sympathectomy was performed 39 times for vascular disease in Division A of the Department of Surgery, Toronto General Hospital. The cases included 2 of Raynaud's disease, 1 of an obscure vascular lesion in a young woman, 13 of peripheral arteriosclerosis and 23 of Buerger's disease.

RESULTS OF SYMPATHECTOMY IN VASCULAR DISEASE AT SURGICAL DIVISION A TORONTO GENERAL HOSPITAL (19 9–1939)

	Goo	Fair	P o		Total
Buerger s di ease	13	7	3		¬3
Arteriosclerosis	5	1	7	(3D)	13
Raynaud s di ease	1		1	(1D)	2
Other conditions	1				1
	¬0	8	11		39

The results were classified as good fair and poor Good results mean striking relief from pain and intermittent claudication increased ability to work and all of this sustained to the present time Fair results mean only slight or moderate improvement in circulation or more improvement which was not sustained or relapse with gangrene after a period of relief Poor results mean little or no improvement obtained by sympathectomy On this basis it is seen that in Buerger s disease a satisfactory percentage of good results was obtained (63 per cent) as well as 30 per cent of fair results Results in arteriosclerosis are not so striking still 40 per cent of good results was obtained Since most of the patients were thus spared amputation it is a result of some importance

Conservative Treatment of Occlusive Arterial Disease Irving S Wright[9] (Columbia Univ) discusses the conservative measures of treatment such as rest active vascular exercises care of extremities abstinence from tobacco alcohol baths soaks heat typhoid vaccine vasodilating drugs tissue extracts mechanical therapy reactive hyperemia and intermittent venous occlusion and the vasoscillating bed

Rest —This is one of the most important factors in treatment of patients with ulceration or gangrene The extremity must be elevated at exactly the right level which is the point at which the tip of the extremity is from 7 to 15 cm below the level of the heart Then gravity assists the flow of arterial blood into the limb and the blood is not retarded in its return by too greatly

(9) N w E gl d J M d 5 80 810 N 0 1941

increased venous back pressure Rest should be continued until the lesion is healed except in other specific vascular exercises

Active Vascular Exercises—A modification of Buerger's method is presented The physician should first elevate the patient's extremity until pallor develops The time necessary for this to occur should be noted He should then lower the extremity until rubor develops and again should measure the time required These times should be given to the patient as indicating the exact periods for elevation and dependency, rather than arbitrary units of time The reactions should be rechecked occasionally and the instructions changed as indicated Allen's modification of Buerger's exercises in which the foot is extended downward and raised by flexion of the ankle joint with the toes turned inward then outward and separated and closed is helpful

Care of Extremities—Meticulous care of skin and nails of extremities with impaired circulation is vital Hands or feet that have not yet developed ulceration or gangrene should be bathed daily and the skin and nails kept soft by application of lanolin or olive oil Nails and calluses must be pared with care Strong dekeratinizers are to be avoided Frequent examination must be made for evidence of epidermophytosis since the cracks produced by this are frequent portals of entry for serious secondary bacterial invaders Soaks of potassium permanganate in dilutions of 1 7 000 to 1 10 000 for 30 minutes every two or three days are satisfactory If ulceration occurs efforts must be made to improve the blood supply rather than resort to surgery Soaks should be used All strong antiseptics must be avoided Gradually by careful daily dissection sloughs and other debris should be removed thus allowing the endothelial epithelial and connective tissue cells to extend in from the edges Purulent material should not accumulate under the scabs Adequate drainage is maintained by removing or cutting windows in the scab followed immediately by a saline soak

If gangrene and then lymphangitis or a septic syn drome develop amputation may be necessary However if the gangrene is developing slowly self amputation may occur and should be permitted since the circula tion is usually adequate for healing at the point of sep aration The points of separation should be kept clean and persistent tendons and other fibrous tissue should be cut a little at a time Finally the digit may be lifted off with little discomfort local anesthesia is contrain dicated If the tip of a phalanx protrudes beyond the level of separation it may have to be removed to that level on the shaft of the bone slowly in small frag ments with a scalpel healing will then be more satis factory After each dressing a 30 minute soak in sterile physiologic saline solution at 96 F insures drainage and cleanliness The area is then dried sterilely and kept under dry thermostatically controlled heat Nerve sec tions should only be used when absolutely necessary

Abstinence from Tobacco—Permanent abstinence is required to prevent spasms in the small collateral branches If the blood supply has been reduced by dis ease to a bare minimum necessary for the life of the tissue it is disastrous to produce repeated spasms in these small vessels and thus reduce the blood supply to a point *incompatible with the life of the tissue*

Alcohol—Alcohol may be recommended as a vaso dilator and sedative It can be taken almost to the point of inebriation during the acute painful periods of ulceration or gangrene and its moderate daily use after the lesions have healed and the patient has again be come active is beneficial

Baths—A modification of the sitz bath in which the patient sits in a tub containing at least 12 in water at 95 to 100 F for 30 minutes once a day is recommended This tends to produce vasodilatation of the vessels from the hips down and is satisfactory provided no open lesions are present

Soaks—These are used two or three times daily for 15 to 30 minutes A boric acid solution or physiologic

solution of sodium chloride at 96 to 100 F is satisfactory The temperature must be kept within these limits After each soak the extremity is carefully dried, and dry heat is applied to prevent chilling and to permit softening of crusts and adequate drainage

Heat —Only controlled heat with the temperature between 88 and 96 F should be used Reflex heat is of value Application of warm pads short wave currents diathermy and the like to various portions of the body not involved results in a tendency toward reflex vaso dilation of the major vessels and their collaterals distally It is of definite advantage and not dangerous

Typhoid Vaccine —The intravenous use of typhoid vaccine is of value in treatment of thrombo angiitis obliterans but not in arteriosclerosis obliterans The H antigen prepared by Eli Lilly and Company recommended by Barker is satisfactory Wright has used typhoid vaccine prepared by the Kirk Biological Laboratories which is diluted to a strength of 100 000 000 organisms per cu cm and given intravenously The first dose should not exceed 5 000 000 organisms The object is to produce a fever of 2 or 3 F without chills When the repeated dose fails to produce an adequate response the amount is increased by 3 000 000 to 5 000 000 organisms, given every three or four days Administration is continued until the ulceration is healed and for several months thereafter to develop adequate collateral vessels

Vasodilating Drugs —These are of rather doubtful value in treatment of occlusive vascular disease

Tissue Extracts —The present relatively pure form of pancreatic extract (depropanex) favorably affects intermittent claudication The material is injected in doses of 3 cc intragluteally two or three times a week

Mechanical Therapy —The pressure suction boot is of value in a few selected cases of arteriosclerosis obliterans in which the lesion is small and not infected and the level of blockage is below the level at which the cuff is applied It should not be used in the presence of thrombophlebitis

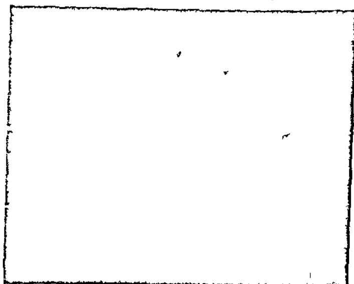
Reactive Hyperemia and Intermittent Venous Occlusion—Wright has used this treatment on 23 cases and the results have convinced him of its uselessness despite various reports of apparent improvement with its use

Vasoscillating Bed—This is valuable in arteriosclerosis obliterans with impending or actual gangrene or ulceration Healing of ulcerations previously obstinate and general improvement in circulation in many cases have been noted Progress is relatively slow and it is frequently necessary to keep the patient on the bed steadily for at least a month After this time the patient may be up and about during the day but he must have eight hours of treatment at night on the bed This is continued over months or even years and it appears to be of real value in increasing the ability of the collateral vessels to take over the burden of the functions associated with tissue nutrition A thermostatically controlled light as part of the equipment with the bed is recommended

Value of Carbon Dioxide Baths in Treatment of Peripheral Vascular Disease and Allied Conditions Experiments conducted by Irwin D Stein and Irvine Weinstein[1] (Montefiore Hosp New York City) show that carbon dioxide by virtue of its chemical properties is capable of producing active hyperemia when in intimate contact with the body surface This hyperemia is localized to the area treated and is unaccompanied by an appreciable elevation of tissue or general metabolism The carbon dioxide bath does cause an increase of blood flow which presumably is chiefly in the superficial layers of the subcutaneous tissue and the skin No proof of deeper penetration or action has so far been found As result of this increase in blood flow the bath is a gentle and effective method of treating selected patients who usually are elderly persons with diffuse far advanced disease but have a fairly good collateral circulation despite pain skin and color changes and occasional superficial necroses The carbon

(1) Am H J 3 349 361 M h 194

dioxide bath is a palliative method which aids in preserving the peripheral circulation by releasing spasm and aiding in production of compensatory circulation and by not increasing tissue metabolism. Its use is also suggested in refractory cases of superficial necrosis vasospastic disease and scleroderma (Figures 115 116)



F g 115 —C p ll r s of nail f ld befo t tm nt with a bon d x de Phot mic og ph f om fi ge of woman, 43 w th ld ula di se f lower nd cl n lly n mal upper ext m ties (Ste n W tein, abo e)

Rational Therapy of Thrombophlebitis Alton Ochsner and Michael DeBakey (Tulane Univ) discuss the etiology and clinical manifestations of thrombophlebitis and present results obtained by procaine hydrochloride block of the sympathetic in 41 cases Vasospasm is the most important factor in the production of the clinical manifestations The mechanism is the initiation of a vasomotor reflex over the sympathetics as a result of impulses originating in the thrombosed venous segment As a result of vasospasm, there occurs increased filtration pressure anoxia of the capillary en

(2) New O lea s M & S J 94 173 178 O t

dothelium and diminution in the lymph flow setting up a vicious cycle Thus the interruption of the vasocon strictor impulses by procaine hydrochloride block breaks the circle by increasing pulsations improving circulation and tissue oxygenation and increasing lymph flow

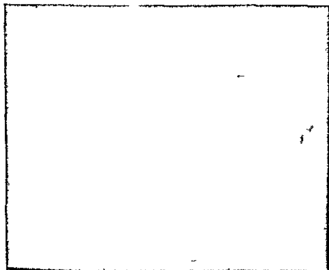


Fig 116 —S m se s p ed g p ll es f n l f ld afte xposur t bo d d b th f n h lf h N te n n umbe f p l) s w ll d l t to f el (w) (St n W nstein, p 657)

Of the 41 patients 35 were permanently relieved bv the first block Only six required a second block Fever subsided rapidly in 48 hours or less Complete sub sidence of edema occurred within four days or less after beginning of treatment in 50 per cent of the cases and within five *to eight days in 30 per cent Hospitalization* time was noticeably decreased

TECHNIC —For lower extremity involvement the patient is placed in the lateral recumbent position with the affected side up The skin is prepared over the lumbar area and wheals are made in the skin by intracutaneous injection of 1 per cent proc [illegible]ochloride at points about 2 to 2½ fingerbreadths

acetate) and benefits impaired coronary circulati which frequently coexists Papaverine in doses of ½ intravenously in early cases of embolism and thrombo is valuable in maintaining and facilitating collate circulation Nitrites choline derivatives and iodic are of some benefit

Indications for sympathectomy in peripheral circu tory disturbances are shown in Table 2 For symp thetic denervation of the upper extremity the pregan lionic sympathectomy of Smithwick has superseded other methods For the lower extremity the lumb ganglionated trunk between the second and the four ganglion is excised, using an anterolateral extraper oneal approach Causes of failure are incomplete d nervation improper selection of cases or postganglion degeneration

TABLE 1—METHODS OF TREATMENT FOR PERIPHERAL VA CUL DISEASE

PHYSICAL	MEDIC L	SU GICAL
Heat	Vaccines	Sympathectomy
Hot and cold bath	Hypertonic solutions	Paravertebral block
Postural exercises	Alcohol	Peripheral nerve blo
Massage	Theobromine	Amputation
Diathermy	Papaverine	
Short wave	Nitrites	
Iontophoresis	Choline derivatives	
Suction and pressure	Iodides	
Venous hyperemia		

TABLE 2—INDICATIONS OF SYMPATHECTOMY FOR PERIPHERAL CIRCU LATORY DISTURBANCES

DIAGNOSIS	INDICATIONS
Raynaud s phenomena	Lack of marked structural changes in th vessels *absence of sclerodactylia*
Buerger s disease	Definite collateral reserve absence o acute inflammation or arteriolar destruc tion poor response to conservative treat ment
Poliomyelitis	Moderate paralysis limited to one ex tremity evidence of vasospastic phenom ena age preferably between 6 and 10
Reflex dystrophy (causalgia traumatic vessel spasm Sudeck s atrophy)	Severe cases resistant to physiotherapy exhibiting exaggerated vasomotor re sponses

Thrombo Angiitis Obliterans Frank V Theis and M R Freeland[4] (Univ of Illinois) report that clinical results in treatment of the biochemical blood changes in acute or active thrombo angiitis obliterans with sodium tetrathionate or sodium thiosulfate and of the peripheral circulatory deficiency due to arterial thromboses with pavaex treatment have been most encouraging Deficient oxygenation of the arterial blood was usually present during the active stage of the disease Following treatment for two to six weeks the increased oxygenation of the arterial blood was accompanied by clinical improvement and in some cases by clinical recovery (five years)

Therapeutic Considerations of Thrombophlebitis and Phlebothrombosis *Alton Ochsner and Michael De Bakey* (Tulane Univ) point out the importance of differentiating between two major types of intravascular clotting thrombophlebitis and phlebothrombosis The clotting in thrombophlebitis is the result of injury to the vascular endothelium from mechanical trauma bacterial invasion or chemical injury whereas in phlebothrombosis the intravascular thrombus formation is due to venous stasis and to alterations in the cellular and fluid constituents of the blood that increase the clotting tendency The prognostic significance of this differentiation lies in the fact that in thrombophlebitis the clot is usually firmly adherent to the vein wall and is therefore less likely to become detached and result in embolism In phlebothrombosis the coagulum is loosely attached to the vessel and is therefore likely to cause embolism The therapeutic significance of this differentiation lies in recognition of the respective processes and institution of appropriate measures to prevent the occurrence of complications and to enhance restitution Such factors as age smoking habits varicosities obesity cancer dehydration anemia and other dyscrasias must be recognized *preoperatively to institute appropriate*

(4) S g y 11 101 117 J ry 194
(5) New E gl d J M d 225 20 224 A g 7 194

prophylactic measures During operation the role of accidental trauma contamination dehydration, circulatory collapse and chilling must be recognized to avoid as far as possible formation of a thrombus

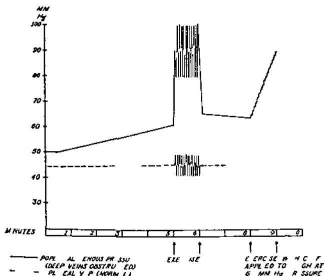
The authors present a comprehensive resume of the therapeutic measures which should be used in superficial and deep thrombosis

Pathologic Physiology of Circulation in Acute Thrombophlebitis and the Post-Thrombotic Syndrome James Ross Veal and Hugh Hudson Hussey[6] (Georgetown Univ) state that the symptoms of acute thrombophlebitis and the post thrombotic syndrome are the logical expression of a regular sequence of alterations in the circulation of the involved extremity The pathologic physiology which underlies these alterations involves all four of the components of the circulatory system namely the arterial venous lymphatic and capillary Comprehension of the pathologic physiology is essential to proper treatment The prime consideration in acute thrombophlebitis must not be recognition of the fact that a clot has formed in a vein but of the fact that all elements of the circulation in the affected extremity are altered as a result of the venous occlusion The degree of this alteration depends on location and extent of the thrombus and the severity of the local inflammatory process in the veins The importance of this viewpoint in the treatment becomes apparent when it is realized that little or nothing can be done to influence the blood clot already formed in certain rare cases it is possible to minimize the danger of embolism by ligation of the vein above the thrombus Treatment in general must be directed to the relief of the changes which take place in all components of the circulation in the affected extremity

Therapy should be primarily intended to correct the stagnation of blood and lymph flow in the involved extremity to prevent if possible propagation of the thrombus Alleviation of stagnation can be obtained

(6) Am H a t J 3 90 409 Ma h 194

by release of vasospasm elevation of the extremity and active movement of the extremity Release of vaso spasm can be obtained by raising the body temperature to a febrile level but if this does not suffice additional measures must be used (Fig 118) because the release must be complete Elevation of the affected extremity above the level of the heart tends to remove the factor



Fg 117—P t tl ombot t g f ıl f m l th mbophl b t N t ext eme el t n e I u ffe t d d d rı g a m p ed t mal fi t t n u ff t d d Ext m ll t n s p u bstruct d s de d g e w ɪp tly d to c mp t y f mmun t g s d m t t d by d pp a ce of w de u s wh n pe fi l we luded by t u n quet

of hydrostatic pressure Emptying of the veins and lymphatics is thereby enhanced Active motion of the extremity by the patient promotes emptying of lym phatics and veins and improves circulation by increas ing rate and volume of arterial blood flow

Treatment of the post thrombotic syndrome should begin before the patient with acute thrombophlebitis resumes normal activities The most important thera

peutic measures are those which encourage development of a collateral channel and tend to prevent overfilling of superficial veins and lymphatics Pressure bandages of some type are useful but arterial circulation must never be impeded by such a bandage A properly fitted elastic stocking is best Active surgical measures which involve any part of the venous circulation have no place in the therapy of the post thrombotic syndrome as long

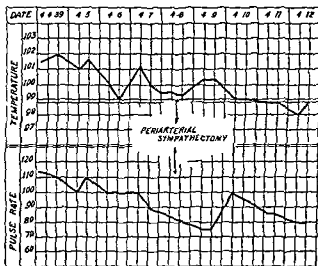


Fig 118 —P tpa tum ıl of n o al thrombophl b t s Acute pa ŋ in l wer part of th gh nd knee cy ı of e tre l g and ab ence f fem ral pulsa t on imul ting arte l mb li m Explorat on of f m l e sel e aled thrombophl b t s w th sp sm of rtery Pe ıa ter al sympath t n y immedi tely restor d pulsat on and rel eved ı hem c pa n

as the venous pressure in the affected extremity is abnormally high at rest or becomes abnormally high during exercise (Fig 117)

In discussing the report by Veal and Hussey A W Duryee states that two further factors influencing development of thrombophlebitis might be considered they are the tremendous variation in the arrangement of the venous system and muscle abnormalities and bone abnormalities in the region of the shoulder which may

obstruct venous return Geza de Takats suggests the use of diuretics for management of acute thrombo phlebitic edema and x ray therapy in small doses in treatment of periphlebitis and lymphangitis

Thrombophlebitis and Pulmonary Embolism Claude E Welch and Henry H Faxon[7] (Massachusetts Gen l Hosp) *state that careful attention must be paid to* correct any abnormalities such as cardiac failure elec



Fig 119 (l ft) —Diff t t n f a p rfi l d d p th mbophl b t s N m l n gr m
Fig 1 0 (ght) —Ven gram f p t nt ft p t wh l lly h d nly s p fl l th mbophl b t N t l k f f m l Imm d te lig t f pe fi l f m l w th m l f th mb R ry w th t mb l m f t t

trolyte *imbalance and anemia Varicose veins should* be ligated preoperatively or controlled by compression bandages thereafter Postoperatively stasis of the blood stream must be avoided This is promoted by fre quent active movements of the legs in bed Elevation of the foot of the bed during the early postoperative period will keep the veins of the calves relatively empty and prevent stasis in this important region

Other measures to prevent thrombosis are of im portance The most recent has been the postoperative

(7) J A M A 11 150 1508 N 1 1941

administration of heparin Bancroft has suggested the use of sodium thiosulfate intravenously and also the use of diets low in protein to diminish the clotting factors The authors have used thiosulfate without striking results so far as dissolution of a previously existing thrombosis is concerned The protein in the blood stream is lowered \\ith such difficulty and only after such pro



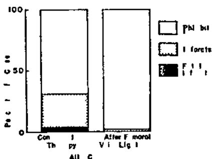
F g 121 (l ft) —Normal v gram
Fig 12 (ght) —Ve gr m of me [t e t as n F gu 1 0

tracted periods that it hardl\ seemed \\ise to persist with this special diet The postoperative use of thyroid to speed the pulse and thereby prevent stasis was tried extensively in the hospital for a year without any clear cut conclusion The authors believe it possesses no definite merit

A few cases can clearly be defined as either phlebothrombosis or *thrombophlebitis but most are equivocal* The term thrombo embolic disease used by many con

tinental surgeons emphasizes the essential similarity of these two types The authors call all cases of intravascular inflammation or thrombosis by the admittedly loose term of phlebitis It is important to recognize however that the more closely the symptoms and signs approach those of true phlebothrombosis the more dangerous is the situation

In superficial phlebitis care should be taken to exclude the presence of deep phlebitis This means that a venogram should be made before operation If the superficial veins only are involved and the patient is not in poor condition ligation and division of the involved saphenous vein at its junction with the femoral or popliteal vein should be performed Heat elevation compression bandages



F 1 3—I d f mbolism w th th mbo- phl b t f l g ft rv t th r py nd ft l g t f f m l

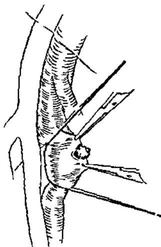
incision and drainage of fluctuant areas and excision of thrombosed venous segments are adjuvant measures

In deep phlebitis not associated with an infarct elevation heat and sedatives should be used Lumbar block with procaine hydrochloride is of value if vasospasm is considerable or pain is severe and perhaps in all cases For patients under 40 no other treatment need be considered unless infarcts occur for the chances of an initial infarct being fatal are extremely remote For those 50 70 early ligation of the femoral vein is indicated in view of the expected mortality of 7 per cent Over 70 there is an absolute indication for venous ligation because the expected mortality from embolus is 20 per cent

In deep phlebitis followed by an infarct the femoral

vein should be opened, thrombi removed and the vein ligated This is necessary to prevent the 10 per cent mortality of the second infarct

In pulmonary infarct without evidence of phlebitis venograms should be done on both sides If a thrombosis can be detected ligation of the corresponding femoral vein is indicated A small infarct with minimal pulmonary symptoms may be treated conservatively If the infarct is severe, heparin therapy should be instituted



F g 1 4—V in op ed f esh th mbus present

Ligation of the femoral vein has appealed to the authors more strongly with added familiarity with the operation At present, the immediate decision to be made in any case of thrombophlebitis is whether the patient should be treated conservatively or by ligation of the vein If conservative therapy is used lumbar injection of procaine hydrochloride should be done if vasospasm is considerable If the deep venous channels are interrupted heparin is often of value when administered postoperatively These concepts may be greatly modified as experience is gained The important fact is that thrombophlebitis is no longer observed passively but is accepted as a disease that must be vigorously treated

In a discussion of this paper Ochsner points out that in phlebothrombosis the patient does not appear very ill but that the condition is potentially dangerous because of the likelihood of embolism The patient with thrombophlebitis appears ill the extremity is swollen and there is much pain The best treatment of thrombo

phlebitis is the overcoming of the vasospasm by procaine block of the regional sympathetic ganglions Ochsner and associates have treated 71 patients with thrombophlebitis Ninety per cent were permanently relieved of pain by the first procaine sympathetic block The subsidence of fever was dramatic About 65 per cent were fever free in 48 hours or less, 24 per cent in 3 to 5 days and 7 per cent in 6 to 8 days 4 per cent had fever more than 8 days The relief of edema was also dramatic Fifty six per cent had normal extremities in 4 days or less 32 per cent in 5 to 8 days and 8 per cent in 9 to 10 days only two patients had edema as long as 12 days All of these were patients with typical phlegmasia alba dolens who otherwise would have had fever and edema for six to eight weeks and a possible persistence of edema for the rest of their lives

Prophylaxis of Pulmonary Embolism by Division of the Femoral Vein Jacob Fine and John B Sears[8] (Harvard Univ) present evidence to show that division of the femoral vein is advisable as routine prophylactic measure against pulmonary embolism when thrombosis of the deep veins of the lower leg is present or suspected (pulmonary embolism arising from auricular fibrillation or any vascular disorder of the venous system cephalad to the great veins in the pelvis is not included) Diagnosis of thrombosis of the deep veins requires careful and repeated examination of the legs for earliest manifestations These are pain or tenderness in the sole of the foot or ankle but usually in the calf muscles pain on forced dorsiflexion of the foot slight fever increased local heat local edema induration fulness of superficial veins and slight cyanosis Unfortunately any or all of these signs and symptoms may be absent and then diagnosis can only be made when the pulmonary embolus discloses its presence

Division of the femoral vein just below the vena profunda is the most desirable method for blocking the discharge of an embolus from the deep veins of the

(8) A S g 114 801 81 Nov mbe 1941

lower leg because no proximal segment of vein with a sluggish stream is left while the profunda and the internal saphenous veins remain as adequate pathways for the return flow of blood The operative exposure necessary for this purpose (Fig 125) permits simultaneous examination of the vena profunda and division of this tributary if it contains a thrombus or clot or if there is preoperative evidence of thrombosis in the deep tissues of the thigh If division of the common femoral is necessary to shut off the vena profunda as well as the femoral vein it may be done only a slight amount of transitory edema due to division itself may result

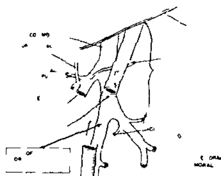


Fig 125 — Anatomy f regi n in l ed n d on f f mo al

Management of Varicose Veins of the Lower Extremities William W Heyerdale and Leonard K Stalker[9] (Mayo Clinic) divide varicosities of the lower legs into three classes from the therapeutic standpoint (1) spider bursts rocket bursts telangiectasic veins (Fig 126) (2) mild or moderate varicosities without associated demonstrable incompetence of the great or small saphenous system (Fig 127) and (3) mild moderate or marked varicosities associated with incompetence of the great or small saphenous system or with incompetence of both systems (Fig 128) About 50 per cent of the patients treated had demonstrable incompetence of the great saphenous system In such cases the essential steps of treatment are ligation and division of the great saphenous vein at the saphenofemoral junction separate division and ligation of the tributaries of the

(9) Ann Su g 114 104 1049 D mbe 1941

saphenous vein and injection of a sclerosing solution into the saphenous system. Pre and postoperative management are important Ligation and division of the offending incompetent vein and injection of a sclerosing agent into it must be meticulously performed to obtain the greatest percentage of permanent results There are six advantages to ligation of an incompetent great saphenous vein (1) Continuity of the vein is interrupted at its most proximal point (2) Possibility of canalization is reduced to a minimum (3) Number of local injections necessary for obliteration is decreased (4) Period of treatment is shortened (5) Adequate complete thrombosis is obtained with greater ease (6) Pulmonary showers are less likely to occur



Fig 1 6 (left) —Diffu sp der b r ts th t l p m ly lat al p t f l w r t m ty
Fig 127 (t) —M ld d mod t n t o l t l a p ct of th gh e t p ct of kn e d i g phe sy t m ot i l ed
Fig 1 8 (ght) —I mpetent g h o y t m w th m d r t co t s N t cirso d d lat t f ph s n t f l

The patient should be instructed when discharged and should be told to expect soreness and tenderness of varying degrees whenever satisfactory thrombosis has

resulted in the obliterated varicosities Other complaints referable to the hard contracting, thrombosed varicosities, such as pulling drawing or sticking sensations stiffness and dull aches may continue for one or two months *The patient should be forewarned not to* become alarmed To give external support an elastic bandage is recommended Follow up examination should extend for six months to a year to detect additional varicosities or regions of recanalization A small amount of sclerosing solution may permanently complete the obliterative process

DISEASES *of the* DIGESTIVE SYSTEM *and* METABOLISM

GEORGE B EUSTERMAN M D

PART V

DISEASES OF THE DIGESTIVE SYSTEM AND METABOLISM

INTRODUCTION

Impressions gained from a review of the world s current literature in this field are as usual instructive and varied The output is less voluminous because most of the medical journals of continental Europe are conspicuous by their absence a fact which is one of the many unheralded examples of the far reaching effect of global war Many articles are appropriately concerned with the problems of military medicine and nutrition The prediction that gastroduodenal disorders and diseases in those inducted for military service would prove to be an entity of paramount importance has been amply realized British authorities state that this entity is the most important medical problem of this war and the largest single type of disease in the armed forces It is estimated that 50 per cent of cases are due to chronic duodenal and gastric ulcer All this, of course is a reflection of what has been going on in the civil population even before World War I It is safe to predict that contributions dealing with the nutrition of war factory workers armed forces in training and in the field and in particular with tropical medicine will appear in increasing volume

Timely articles deal with the pathogenesis of alimentary azotemia and the therapy of hypoproteinemia Sustained interest in diagnosis and treatment of disorders and diseases of the small bowel intestinal obstruction and acute appendicitis which still inexcusably continues to be a major menace is reflected in the numerous contributions on these subjects Our traditional conception

of alcohol in its relation to gastritis needs revision in the light of contemporary gastroscopic research The electrogastrogram gives rich promise of being an effective means of differentiating benign and malignant gastric ulceration

Surgical contributions convey the impression of at least one definite trend namely increasing attempts at removal of the more inaccessible carcinomatous lesions involving the esophagus pancreas ampulla of Vater and upper portion of the stomach Improvement in surgical technic and progress in our knowledge of anatomic and physiologic problems involved make possible advances through more effective preoperative preparation and postoperative treatment and the ability to cope more effectively with the formidable complications which may arise To what extent innovations will eventually prove feasible remains to be seen until we have the means of detecting carcinoma at an earlier stage

—George B Eusterman

Theory Concerning the Manner in which the Stomach Empties Itself William Travis Gibb Jr (New York City) points out that the actual mechanics by which the stomach empties itself have never been explained clearly The stomach is divided into three portions the antrum body and fundus The antrum is that portion which lies distal to the incisura angularis and the musculus sphincter antri the body is the remaining portion except for that part above the cardia which is called the fundus This latter portion contains the air bubble When it is empty the walls of the stomach lie in close apposition Normally however they enlarge enough to accommodate the amount of material placed therein and there is no increase of pressure due to stretching or contraction of the walls When filled with food the body of the stomach acts as a reservoir in which the food is retained and gently mixed by shallow peristaltic waves which start in its upper portion and progress caudally If the stomach is carefully observed over a considerable period waves can be seen going in an opposite direction Other factors probably help in the mixing process Normally the muscles of the abdominal wall are contracting and relaxing frequently and must exert some alternating pressure on the filled stomach The movements of respiration must affect the stomach as well These factors assist in bringing the contents of the body down to the antral region

When food is in the antrum it is further kneaded by the far more powerful contraction waves found there When the duodenum is ready to receive some of the contents of the stomach or when the contents are in the proper state for passage to the duodenum there is a contraction of the musculus sphincter antri which divides the stomach into two distinct compartments This

(2) A Int Med 16 94103 J ry 194

contraction must necessarily involve a large mass of muscle which shortens the antrum and, when closure is complete, raises the hydrostatic pressure of the antral contents There is also at this time what might be termed a systole of the antrum that is the muscle of the antrum contracts and exerts still more powerful hydrostatic pressure The pylorus is open at practically all times, thus with the junction of the body and antrum of the



Fig 129 (left) —Duodenal ul e produced in dog by int muscular injec ion f h tamine-b swax m xtu l ge crate s produced in x d ys by d ly nject on of 30 mg h stam e
Fig 1 0 (ght) —Typ al hron c du d n l ulcer w th d p excavat on p o du d n dog ft r 30 da ly nject ns of h t mine base (H y t al p 681)

stomach closed the liquid food is literally squirted into the duodenum and cap under considerable pressure Shortly after this so-called systole starts, the usual con traction wave starts just distal to the musculus sphincter antri The wave tends to keep the current of liquid going in the same direction even though the pressure from the systole is relieved When the wave arrives at the sphincter, the pylorus closes and reflux is prevented This theory includes only the mechanics and hydrody namics involved

Emptying Time of the Stomach of Old People Be cause there is a decided lack of quantitative informa tion concerning important functions of the digestive system of the aged Edward J Van Liere and David W Northup[3] (West Virginia Univ) determined the effect of the aging process on gastric emptying Twelve men, the youngest 58 and the oldest 84 were studied Ten were indigent and resided in the county infirmary

(3) Am. J Phy l 134 19 No ember 1941

one was a college professor and one was a janitor

METHOD—At 7 30 a m. they were given a high carbo hydrate test meal, consisting of 15 Gm Quaker Farina and 350 cc water, boiled together and evaporated to 200 cc 50 Gm. barium sulfate was added to determine the position of the meal fluoroscopically No food had been eaten since the preceding evening The men were instructed to relax mentally and physically but could walk around if they desired With the exception of two subjects, at least three determinations of gastric emptying time were made on each individual at exactly weekly intervals, to establish the mean for each subject Emptying time as ascertained fluoroscopically was determined to the nearest 10 minutes



Fig 131 —P fo ti g j ju al ul d g st j ju l ul n imm d t juxt p t n t t m p du d n d g with g t j ju t my ft 13 d ily nject n f h tam ne b

The average length of time for the test meal to leave the stomachs of the 12 men was 1 94 hours with extremes of 1 33 and 2 75 hours The median value was 2 04 hours The gastric emptying time of 59 young adults studied previously averaged 2 08 hours with extremes of 1 03 and 3 08 hours and a median value of 2 06 hours Obviously there is no significant difference between gastric emptying times of the two groups

Experimental Production of Gastric and Duodenal Ulcers in Laboratory Animals by Intramuscular Injection of Histamine in Beeswax Lyle J Hay Richard L Varco Charles F Code and Owen H Wangensteen[1]

(1) S g Gyne & Ob t 75 1 0 18 A gu t 1942

(Univ of Minnesota) describe their method of provoking prolonged maximal secretion of hydrochloric acid from gastric pouches of dogs The method consists in embedding histamine in beeswax, *to permit gradual liberation of the histamine* on intramuscular injection of the mixture With this method gastric and duodenal ulcer may be produced with some regularity in a number of common laboratory and domestic animals The ulcers pro-



Fig 13 —La ge bleed g gast ul t j nctu e f mu osa of a trum and c rp o u d n d g aft f r d ly inject s f l tami e b e

duced appear not unlike those which occur spontaneously in man The manner of producing experimental ulcer furnishes *additional testimony to the great importance* of acid in the genesis of ulcer The method provides a simple means of evaluating the worth of therapeutic agents in retarding or favorably influencing the healing of ulcer Furthermore it affords the surgeon a method of determining experimentally what operative procedures performed on the stomach for relief of ulcer

may most satisfactorily thwart the ulcer diathesis and obviate the recurrence of ulcer postoperatively

Clinical Indications for Inducing Gastric Hypomotility The motor activity of the human stomach is of demonstrable clinical significance particularly in patients with lesions involving viscera innervated by the extended vagi Moreover it appears that the clinical management of certain patients may often be aided by an increased knowledge of stomach activity Frank E

Fg 133—Eff ct f trop e (g t 1) mot l ty f n rm l hum t m h nd l f th ff t by morph (gi n t 2) Low ed t us d d e d g 1 t ty f ll w d dm t t f t p (C rt y f J l f Ph m l gy nd E p m t l Th p t)

Hamilton and George M Curtis[4] (Ohio State Univ) demonstrated hypermotility of the human stomach by the balloon and kymograph method during the clinical appearance of gas pains late postoperative nausea pylorospasm due to obstructive duodenal ulcer biliary colic the nausea and regurgitation associated with advanced carcinoma of the stomach certain instances of hypothyroidism and vagotonia In all patients gastric hypermotility occurred simultaneously with the varying degrees of clinical distress or discomfort The patients ceased to complain of pain or discomfort when the stomach was quiescent Whether the gastric hypomotility was spontaneous or induced by administration of atropine (Fig 133) made no apparent difference At onset of hypomotility the patients ceased to complain of distress In postoperative abdominal cramps interpreted as

(4) J A M A 117 2 8 33 D 7 1941

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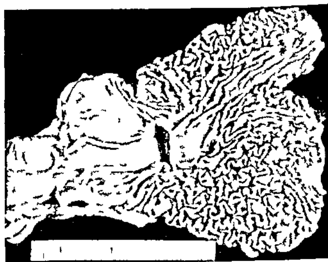


Fig 132 —L ge bleed g gast c ul t ju t e of muc of a trum a d c p o c rred d g afte fo d ly inject s of h tam ne base

duced appear not unlike those which occur spontaneously in man The manner of producing experimental ulcer furnishes additional testimony to the great importance of acid in the genesis of ulcer The method provides a simple means of evaluating the worth of therapeutic agents in retarding or favorably influencing the healing of ulcer Furthermore it affords the surgeon a method of determining experimentally, what operative procedures performed on the stomach for relief of ulcer

In patients with gastroduodenal ulcer the author found the amount of histamine in the blood to be increased before gastric resection and 24 hours after it in most cases the figures of the last determination were lower than those of the first The amount of histamine in the stagnant fluid rose slowly during the first 10 hours after resection and more rapidly between the tenth and the twenty fourth hour after which it slowly diminished The highest figures varied between 0 006 and 0 02 mg histamine per cubic centimeter of the fluid The toxicity of the stagnating fluid is due to its histamine content obtained from the gastric walls by the operative trauma and stimulation of secretion The post operative illness is a form of histamine poisoning the result of gastro intestinal absorption of the stagnant fluid Aspiration of the gastric contents is imperative to prevent postoperative complications

Use of *Topfer s Reagent in Gastric Analysis after* Test Meals of Milk, Cream or Soy Bean Biscuits George B Lawson J R Leonards and A D Pratt[6] (Virginia Polytechnic Inst Blacksburg) report that in testing a patient with duodenal ulcer with various foods to determine possible decrease in gastric acidity it was found that milk would give about one half as much free acid as the bread test meal using Topfer s reagent as the indicator Soy bean biscuits also decreased the acidity Casein and whey were then used but neither showed any apparent change in the total free acid Sweet cream was given after which no free acid was indicated by Topfer s method in the fractional test meal There was further more no change of acidity indicated when an excess of hydrochloric acid was added to cream in vitro Preliminary experiments on titration of milk and cream with hydrochloric acid using Topfer s reagent as the indicator suggested that the indicator did not function properly in the presence of these substances Experiments to determine the action of the indicator showed

(6) J Lab & Clin Med 7 111 112 Oct 1941

'gas pains,' an intravenously administered dose of 1/150 gr atropine was sufficient to produce immediate partial inhibition of gastric motility, accompanied by relief of cramps and pain In patients with duodenal ulcer and late postoperative nausea, the same dose produced decreased motility and relief from pain In continuous nausea and regurgitation associated with partial obstruction of the stomach due to an advanced carcinoma a total of 1/43 gr atropine had to be administered within a short time to produce decreased motility accompanied by subjective comfort

The authors conclude that the motility of the human stomach may be regarded as an indicator of certain types of abnormal activity of the gastro intestinal tract Control of the gastric hypermotility in such instances will often simultaneously control the clinical symptoms associated with the primary condition

[To stress the significance of hypermotility of a hollow viscus is a relatively new departure in medicine In the past and rightly so physicians and surgeons alike have recognized the importance of delayed emptying of an organ whether as the result of a morbid physiologic process or of a purely mechanical one and the inevitable necessity for its correction when present The authors herewith present a *somewhat novel* and perhaps neglected or heretofore unrecognized aspect, of abnormal gastro intestinal function giving rise to disturbances demanding correction —Ed]

Histamine in Stagnant Gastric Secretion after Resection L Busineo and Renato Scoccianti[5] discuss the role of histamine in the pathogenesis of gastroduodenal ulcer and postoperative disease They maintain that an increased amount of histamine in the blood is an etiologic factor in gastroduodenal ulcer Postoperative complications such as collapse peripheral hypotension changes in the blood chemistry and acidosis are similar to the manifestations produced by experimental histamine poisoning Gastric secretion in patients with gastroduodenal ulcer, 24 hours after gastric resection shows an abundant, highly toxic dark fluid stagnating about the operative field unless withdrawn by aspiration

(5) M e va med 1 4 9 435 M y 4 1941

[Patients undergoing the Sippy type of treatment for gastric and duodenal ulcer often are submitted to aspiration of the gastric contents and titration of the latter at stated intervals. In the light of this investigation it is apparent that improper conclusions may be drawn as to the degree of neutralization following feedings with the familiar milk cream mixture.—Ed.]

Observations on Oral Administration of Citrated Blood in Man. Effect on Stools. In management of patients with hematemesis or melena it is important to determine the severity of the hemorrhage and whether the bleeding has stopped. The clinician may assume that the patient has had a severe hemorrhage because he has passed a tarry stool and that he is still bleeding because he continues to pass tarry stools or because his stools continue to give a positive chemical reaction for occult blood. To test the validity of this assumption, Leon Schiff, Richard J. Stevens, Nathan Shapiro and Sander Goodman[7] (Univ. of Cincinnati) gave patients and normal controls known amounts of citrated human blood either orally or by stomach tube and observed the effect on the stools.

Tarry stools were obtained in individuals given 100-200 cc. blood (Table 1). *The four individuals who* passed a tarry stool after 100 cc. blood did not pass such stools when given 50 or 75 cc. blood, while the other five who passed tarry stools did not do so when given at least one smaller dose than the one which produced the tarry stool. The designation tarry was applied only to a glistening stool having the same black color as found on a standard paint color chart.

Following intragastric administration of citrated blood in amounts from 1,000 to 2,000 cc., the blood may appear in the stools within four hours and the stools may be entirely bloody and never tarry, presumably as a result of intestinal hypermotility. Three of the four persons receiving 1,000 cc. blood had no tarry stools whatever (Table 2), the stools possessing a reddish cast, following which they became a dark brown. Thus a

(7) Am. J. M. S. 203:409-41, March 1942

that the fat and/or proteins of milk interfere with the use of this reagent as an indicator in the titration of milk with hydrochloric acid An investigation was made to determine whether the fat or the protein was responsible for this interference Fresh skim milk was obtained which contained less than 0 02 per cent fat On titration with hydrochloric acid, Topfer s reagent functioned normally and changed at the proper pH Thus apparently casein was not the interfering factor Then a sample of 20 per cent cream was acidified in the presence of an excess of Topfer s reagent and centrifuged. The serum was pink but the fat protein layer had a yellow color The casein was then removed by washing three times with N/10 sodium hydroxide once with water twice with N/10 hydrochloric acid and once again with water After this treatment the fat layer still retained the yellow color Possibly in this two phase system the ionization of the Topfer s reagent in the fat phase is negligible

METHOD —Soy bean meal 10 Gm, was suspended in 90 ml distilled water and titrated with hydrochloric acid in the presence of Topfer s reagent During titration, the reagent remained yellow even after the pH was as low as 2 1 as determined potentiometrically Again on addition of 1 ml concentrated sulfuric acid the reagent turned red In this case however it was noted that if during the titration 1 drop of the solution was removed and tested with Topfer s reagent on the spot plate, the indicator turned red at the proper pH This again indicated that some constituent of the soy bean meal interferes with the use of Topfer's reagent

The pH range over which Topfer s reagent changes color is wide and thus even at best the use of the reagent is inaccurate This fact coupled with the interfering substances in milk cream soy bean flour and possibly other common foodstuffs makes the use of this reagent inadvisable in gastric analyses involving these foods In routine gastric analysis where the meal of bread and water is fed it was found that Topfer s reagent was satisfactory and agreed with potentiometric titration

electric graphs thus obtained is variations in the volt age of the so-called gastric T wave These variations are in close correlation with histopathologic changes of the gastric wall as demonstrated by the author in 66 cases

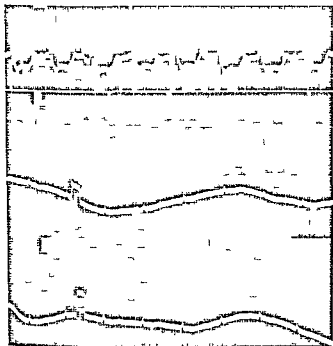


Fig 134 (t p) —G t S T s gm t h w ry h gh lt g
Fig 135 (b tt m) —C f g t t S T gm nt em s l tri

No attempt is made to explain this phenomenon from the pathogenic or the physical viewpoint since the significance of the T wave has not yet been completely clarified even by cardiologists

Gastric Cancerization by Ingestion of Tobacco Tar A H Roffo[9] (Buenos Aires) used 20 rats for his experi

68 April, 1941 (9) B l I t d d xp [l tud y t d d á 18 9

grossly bloody stool does not necessarily indicate that the blood is entering the intestinal tract low in the small intestine or in the colon

Positive chemical tests for occult blood in the stools may persist for as long as 10 days after ingestion of 250 cc citrated human blood or for 12 days after intra gastric administration of 2 000 cc The authors conclude that passage of a tarry stool does not necessarily indi cate the occurrence of a severe hemorrhage into the digestive tract Persistence of tarry stools or occult blood in the stools does not necessarily indicate continu ation of such hemorrhage

TABLE 1 —AMOUNT OF CITRATED BLOOD REQUIRED TO PRODUCE A TARRY STOOL

Blood Given Cc	Subjects Given Blood	No with Tarry Stools	No without Tarry Stools
50	7	0	7
75	9	0	9
100	7	4	3
125	3	1	2
150	4	1	3
175	2	1	1
200	2	2	0

TABLE 2 —APPEARANCE AND DURATION OF BLOODY OR TARRY STOOLS AFTER INTRAGASTRIC ADMINISTRATION OF CITRATED BLOOD

Subject	Blood Given Cc	Appearance of 1st Bloody Stool Hr	Appearance of 1st Tarry Stool Hr	Duration of Bloody or Tarry Stools Days	No of Bloody or Tarry Stools
W S	1 000	12	—	1	3
S W	1 000	17	—	1	3
F O	1 000	4	—	3	4
J G	1 000	9	20	3	5
C E	1 400	4	24	5	8
F F	2 000	—	20	4	3

Electrogastrogram A new modification of electro gastrography has been devised by J Menendez Feros [8] In introducing a conductive and standard buffer solu tion into the stomach by means of especially constructed rubber tubing he obtains bipolar diphasic intragastric deflections of the galvanometer The constant feature of

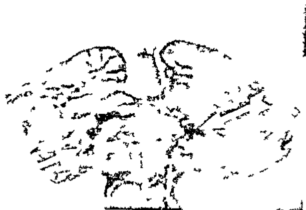
(8) Arch. Soc tud clin Haba a 5 871 88 1941

Here is thus a relation between agent and histologic process under the influence of the same cellular stimulant and in addition a somewhat nearer approach to the human pathology of the smoker because a great deal of the tar which condenses after cooling of the tobacco smoke is deposited in the mouth gets mixed with the food and is ingested with the saliva The action of the tar is not due to its alkaloid but to its hydrocarbons which present a close similarity in fluorescent and spectrographic characters with other cancer producing hydrocarbons In this connection Roffo has succeeded in isolating among other numerous components the active principle of tobacco tar According to the determination of its crystallization fluorescence and absorption spectrum in ultraviolet light it is a substance having the properties of 1 2 benzpyrene The action of tabagism in the development of human cancer seems to be due to *this substance*

New Gastroscope with Controllable Flexibility Experiments carried out by Hermon Taylor[1] (London Hosp) during the last three years have resulted in construction *of a new gastroscope the flexible part of* which can be actively curled up or allowed to lie flaccid at will Passively flexible in all directions for introduction it can be bent forward and backward in the plane of the objective up to the limits of optical flexibility This property endows the new instrument with several advantages First it enables the operator to overcome certain of the causes of failure of gastroscopy With the Schindler instrument unsuccessful results were obtained in 9 per cent of a series of cases Most of these failures were due to a high lesser curve lesion which either by its size or by the distortion it caused presented an insuperable obstruction to the passage of the instrument No amount of manipulation of the proximal end could alter the lateral position of the flaccid distal part and since force could only result in dangerous trauma there

(1) L t 2 276 2 7 S pt 6 1941

ment The initial lesion was always a simple hemorrhagic ulcer which became necrotic turned into rodent ulcer and finally became a real cancer The daily doses of tar given were minimal and nontoxic as shown by the survival of most animals some reaching an age of over 2 years The gastric lesions developed in 50 per cent of



F g 136—Adeno ar n ma of stomach Arr ws show tw ulce at o s w th nfilt ted and veget t g bo d mo t l te t ng sp m n be use of evol t n of n opl t f mat on wh h d t y d e en e t rnal m sc lar l y

the animals and involved essentially the glandular zone although some hyperplastic papillomatous lesions were also found in the squamous zone and the epithelial border fold Cancerization of the lesions occurs late the first signs of malignancy appear one year after the beginning of tar ingestion this corresponds to the time relation previously observed in the production of carcinoma on the ears of rabbits by applications of tobacco tar

rigid part to be lengthened as compared with the Schindler instrument. The resulting reduction in the number of short focus collecting lenses in the flexible part of the optical system has resulted in a considerable increase in the light-transmitting power and hence in a greatly enhanced brilliance of the endoscopic picture

INSTRUMENT —It is 30 in long over all and has a 1 in longer internal reach than the Schindler gastroscope a property useful in tall patients with gastroptosis The flexible part consists of two concentric metal tubes constructed of left and right hand spirals respectively and the movement i controlled by two longitudinal wires between them at the back and the front of the instrument A push and pull action of the wires controlled by a differential rack and pinion mechanism near the eyepiece imparts the required degree of curvature to the flexible part but when the controlling wheel is free the instrument lies flaccid The lamp is incorporated in the rounded tip of the instrument and the whole is streamlined for smooth movement down the esophagus The electrical and pneumatic connections are combined at the upper end of the instrument so that only one attachment need to be made to the instrument after it has been introduced into the stomach

Hiatus Esophageal Hernia with Special Peference to a Comparison of Its Symptoms with Those of Angina Pectoris In a series of observations on 128 patients with diaphragmatic hernias Chester M Jones (Massachusetts Gen l Hosp) particularly considers the symptomatology The nature and incidence of various symptoms are shown in the table Obviously hiatus hernia may engender symptoms closely simulating those of serious heart disease

To distinguish hernial from cardiac symptoms Jones points out certain features (1) pain referred to the right shoulder is frequent in hiatus hernia (19 of 45 cases) and relatively uncommon in angina pectoris (2) exertion does not consistently precipitate pain in patients with hernia whereas dietary and alcoholic indiscretions or emotional tension or a combination of these

(2) N w E gl d J M d 5 963 97 D 18 1941

was no alternative to abandonment of the examination in these circumstances With the new instrument, how ever the end can be lifted clear of the obstruction and guided safely onward under vision into the cavity of the stomach when inspection can be completed Further the lateral mobility of the objective permits a much more detailed examination of the mucosa to be made by approaching or withdrawing from any particular area at will The mucosal surface is always in focus, and the degree of magnification of any part can be controlled by adjusting its distance from the objective Thus a

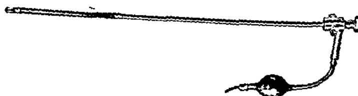


Fig 13 —Gastroscope

near view of the pylorus can be obtained More proximally the objective can stand back from the posterior wall to provide a more comprehensive view of it than can be obtained by the close approximation at which the passively flexible instrument naturally lies The property of active flexibility carries with it the ability to alter the intragastric angle of view of the objective which becomes retrograde when the instrument is curled forward and prograde when it is bent backward The intragastric field is therefore no longer limited by blind areas for example the roof of the pyloric antrum in the J shaped stomach is now visible by the combined effect of approximation of the objective and retrograde deviation of the angle of view brought about by flexing the instrument Active control of movement has permitted the flexible part to be shortened and the upper

tion probably by tension and traction exerted on the hernial orifice by the distended viscus contained therein

Treatment of the symptoms of the smaller hiatus hernias is essentially medical Phrenicectomy or surgical repair is justified in large hernias or where medical measures have failed Light bland small meals taken frequently antacids antispasmodics such as atropine belladonna or trasentin and nitroglycerin for the acute attacks are recommended An upright or semi upright position after eating is desirable Another important therapeutic consideration is the proper evaluation of coronary heart disease and cholelithiasis when either condition is associated with the hernia

[This is an instructive contribution to our knowledge of an increasingly important entity and should be read in its entirety The article is distinguished for its emphasis on the clinical importance of the small (hiatus) hernia for the detailed comparison of its symptoms with those of angina pectoris and for an enlightening discussion of the pain mechanism Considering the well known and commendable conservatism of the author it must have taken a good deal of courage to go on record as saying that small hiatus hernias have a reasonably characteristic set of symptoms which under careful observation can be properly diagnosed —Ed.]

Diagnosis Incidence and Significance of Essential Achlorhydria Achlorhydria is not only of importance in pernicious anemia but is also prominently involved in such conditions as gastric carcinoma chronic gastritis gallbladder disease Graves s disease tuberculosis gastrogenous diarrhea alcoholism subacute combined sclerosis anorexia nervosa sprue pellagra gastric syphilis Simmonds disease and achlorhydric anemias Asher Winkelstein[3] (Columbia Univ) suggests that the terms anacidity and achylia gastrica should be dropped and false or true achlorhydria adopted By true is meant one that is complete more or less permanent and with a pH of 3 5 or over The Ewald and Riegel test meals the oat meal gruel fractional test meal or the histamine test alone are insufficient to establish the diagnosis of true achlorhy

(3) Am J M Sc 03 419 4 8 M h 1942

factors do (3) nocturnal attacks with the patient in the recumbent position are not uncommon in hernia, (4) the act of lying down or bending forward provokes pain in almost half the patients with hernia (5) the consistent use of atropine affords frequent and striking relief in hernia whereas relief from nitroglycerin may be dramatic or fail entirely

DISTRIBUTION OF SYMPTOMS

Symptom	Small Hernias		Large Hernias	
	Hospital Patients (46)	Private Patients (45)	Hospital Patients (3)	Private Patients (5)
Substernal pain	9	25	4	1
Shoulder pain	16	8	8	1
Arm or hand pain (or both)	2	6	3	1
Palpitation	4	2	3	1
Dyspnea	7	2	10	2
Cough	0	0	0	0
Epigastric pain	31	19	21	3
Costal margin pain	16	5	10	1
Subscapular pain	0	4	0	0
Axillary pain	1	2	0	0
Back pain	12	9	9	1
Vomiting (or regurgitation)	36	15	21	3
Heart burn	1	14	1	0
Dysphagia	0	3	1	0

The pain of hiatus or diaphragmatic hernia is mediated over visceral afferent fibers supplying the esophagus and the cardiac or fundic portion of the stomach or over the sensory afferent fibers from the diaphragm contained in the phrenic middle or lower thoracic nerves Overflow to adjacent low cervical or low thoracic segments undoubtedly occurs Overdistention of the lower end of the esophagus or the herniated portion of the stomach with or without an associated localized esophagitis or gastritis may thus be responsible for the production of anginal pain in any or all of its components The shoulder pain is largely due to diaphragmatic irrita

acid pepsin irritation and toxic infectious factors chiefly from the nose, throat and teeth may play important roles in the genesis of gastritis

[This is a critical review of the subject by a capable worker, which again stresses the importance of differentiating an actual from an apparent achlorhydria. I fear that the prophylact c meas ures advocated are a coun el of perfection. Because of the in convenience time and expense involved and the fact that many patients are symptomatically well periodic check up and preven tive measures will be neglected —Ed]

Chronic Alcoholic Gastritis Leonidas H Berry[4] (Chicago) states that evidence from the literature on attempts to produce chronic alcoholic gastritis in experimental animals shows that in some instances a transient super ficial type of gastritis has been produced but that in many others no gastritis has been produced Pathologists have supplied no evidence in the literature of unequiv ocal chronic gastritis due to alcohol Hirsch observed frequent gross and microscopic petechial or ecchymotic hemorrhages but no inflammation No previous gas troscopic study of alcoholic addicts has appeared in the American literature The one report in the foreign literature on 45 patients described extensive atrophic gastritis however Berry believes that this was probably not due to alcohol directly

Gastroscopic studies on 100 persons with unquestion able chronic alcoholism of long standing showed 30 per cent without gastritis 35 per cent with mild chronic superficial gastritis with a gastric mucosa only slightly different from normal and only 35 per cent with un equivocal chronic gastritis

Gastric Mucosa of Chronic Alcoholic Addicts A Gastroscopic Study There are two conflicting schools of thought concerning the effect of chronic alcoholism on the gastric mucosa One group of observers empha sizes the injurious effect of alcohol on the stomach while the second group believes that alcohol does not play an important part in causing chronic gastritis

(4) J A M A 117 2 33 236 D 27 1941

dria A combination test including oatmeal gruel, histamine and neutral red seems more efficient in diagnosis of true achlorhydria Using this procedure Winkelstein found that the incidence of true achlorhydria unassociated with the organic diseases usually accompanying true achlorhydria is extremely low, namely 1 2 per cent thus indicating that true achlorhydria of undetermined etiology is rare in young or old individuals Since true achlorhydria is so often associated with definite organic diseases, its presence should indicate a thorough search for such diseases If they are not found certain prophylactic measures against the gastritis probably causing the achlorhydria should be instituted in an attempt to prevent subsequent development of these diseases In general people from 35 years up should be advised to have a test meal roentgen examination and possibly a gastroscopic examination every 6 to 12 months regardless of whether they have symptoms or not If achlorhydria or other evidence of gastritis is found prophylactic and therapeutic measures such as diet gastric lavage liver and iron should be instituted After some improvement administration of hydrochloric acid and pepsin may be indicated Hurst an advocate of this plan believes that it would give earlier diagnoses of pernicious anemia achlorhydric anemia, gastric carcinoma chronic gastritis chronic gallbladder disease and Graves s disease would help in some measure to prevent these anemias would cure or retard chronic gastritis and finally by perhaps decreasing both the atrophic and the hyperplastic reparative phase of the inflammation would lessen somewhat the incidence of gastric carcinoma

Winkelstein believes that gastritis may be the chief cause of achlorhydria and that henceforth the inflammatory states of the stomach should receive close attention There may be many varied causes for the gastritis Probably certain functional states such as pylorospasm retention, atony hypertonic states myospasm vasospasm

essentially normal in 55 of 100 men who consumed an average of about 3 pt alcohol daily for over 20 years

Superficial gastritis an inflammation of the stomach characterized by patches of thick gray adherent mucus covering an edematous and irregularly colored mucosa was the commonest disease observed in the remaining 45 men it was seen in 30 The gastritis was mild in 10 in which only small patches of mucus were seen and was more severe in 14 in which larger areas were involved In six men the gastritis was so severe that the entire mucous membrane appeared to be covered with grayish white adherent mucus Large sheets of mucus hanging from the gastric walls covered the mucosa so completely in one man that no mucous membrane whatever was discernible Simple superficial gastritis and superficial hemorrhagic gastritis were each seen in nine men Superficial erosive gastritis and superficial hemorrhagic erosive gastritis each occurred in two men and combined superficial and atrophic gastritis appeared in eight Antral gastritis appeared infrequently and then only in conjunction with gastritis of the body of the stomach with which it was seen in seven men In the remaining 23 men the antrum and the pylorus were normal and the superficial gastritis was confined to the body of the stomach Atrophic gastritis was found in 21 men The gastric mucosa in these was thin and gray and networks of purplish blue blood vessels could be seen through the atrophic mucosa The stomach was almost completely atrophic in eight men in which huge protruding branching blood vessels with severe thinning and graying of the mucosa could be seen Simple atrophic gastritis was seen in eight men and hemorrhagic atrophic gastritis in three Polyps were noted with atrophic gastritis in two men and the atrophic gastritis was combined with superficial gastritis in eight In these patches of thick gray adherent mucus were observed superimposed on a thin gray mucosa interspersed with arborizing blood vessels Usually the superficial gastritis was more pronounced in

Gross descriptions of the stomach have been highly unreliable because of postmortem autolysis, and microscopic sections have been made infrequently while animal experiments have not been conclusive It is only with the advent of gastroscopy i e direct visualization of the living gastric mucosa that gastritis can be diagnosed without error

Seymour Gray and Rudolf Schindler[5] (Univ of Chicago) examined 100 men with chronic alcoholism gastroscopically Duration of alcoholism ranged from 3 to 52 years with an average of 21 1 years Twenty three men had been drinking for 10 years or less and 77 gave a history of alcoholism of 10 to 52 years' duration The group consumed an average of 2 4/5 pt alcohol daily 53 drank 2 6 pt daily, and 44 had drunk 1 2 pt daily for more than 20 years Detailed study of the diets showed that fresh fruits vegetables milk and butter were appreciably deficient in every case The typical diet consisted of bread small amounts of meat an occasional egg and large amounts of coffee Vitamin C content of the blood was abnormally low and a deficiency of vitamin B_1 was found in all but 1 of 15 men studied Gastroscopic examination revealed an entirely normal stomach in 43 of the 100 men The gastric mucosa presented no evidence of inflammation hemorrhages or erosions and the soft orange red pliable mucosa could not be differentiated in any way from that in a large control series of normal stomachs The stomach was found essentially normal in an additional 12 men the gastric mucosa being normal except for an occasional small mucosal hemorrhage a pigment spot lying in normal mucosa or a single tiny erosion or a small patch of adherent mucus on normal mucous membrane The pathologic change was so small and the underlying mucosa and the remaining portion of the stomach so healthy that the stomach was classified as essentially normal Thus the gastric mucosa was found normal or

(5) J A M A 117 1005-1011 Sept 20 1941

superficial gastritis and 5 atrophic gastritis No correla tion was observed between the incidence and severity of the gastritis and the duration of the alcoholism the amount of alcohol drunk abuse in the use of nicotine dental infection or vitamin deficiency The authors conclude that although the prolonged use of alcohol seems to produce chronic gastritis in some persons and has no effect whatever on the stomachs of others the rea son for this discrimination is still unknown

Hemorrhage from Gastritis Edward B Benedict[5] (Massachusetts Gen l Hosp) offers proof from autopsy and surgical material that severe even fatal hemorrhage



Fig 139 —S m p d ng R t d p m n m ked l k yt nfilt t n nd pil ry g g m nt I t mu s l urf

may occur from gastritis alone in the absence of other demonstrable pathologic conditions Gastroscopic evi dence of gastritis as the only source of bleeding was pres ent in 42 clinical cases Gastroscopic evidence of gas tritis as a possible source of hemorrhage was present in 24 additional clinical cases with ulcer or with question able ulcer Bleeding may occur from superficial atrophic hypertrophic or postoperative gastritis Bleed ing occurred in 42 of 213 cases of gastritis an incidence

(5) Am. J Roentg ol 47 254 61 F b uary 194

the lower portions of the stomach, and the atrophy appeared more extensively in the upper portions, but in some stomachs patches of superficial gastritis were distributed extensively throughout. Mucosal hemorrhages occurred in 22 of the 100 men studied a rather striking high incidence Most of the hemorrhages were small and were situated in a normal mucosa unassociated with any other pathologic conditions They were usually round and discrete and varied from red to dark brown Not more than two hemorrhages or pigment spots occurred in any of the stomachs Hemorrhages were observed with other gastric disease in 14 cases 9 of superficial hemorrhagic gastritis 2 of superficial hemorrhagic erosive gastritis and 3 of atrophic hemorrhagic gastritis The stomachs of nine men with superficial hemorrhagic gastritis presented numerous large, red diffuse hemorrhages interspersed with smaller punctate discrete red and brown hemorrhages scattered over a swollen mucosa covered with patches of thick grayish white adherent mucus Moderately severe and severe gastritis were accompanied by definite symptoms in 60 per cent while only 7 per cent of the alcoholic addicts with normal stomachs had gastro intestinal complaints In the latter, the symptoms simulated bowel distress



Fig 138 —Marked widening of gastric rugae Diagnosis chronic gastritis (Benedict p 701)

Free acid was present in the secretion of 38 of 63 patients during fasting Superficial gastritis was found in 16 and atrophic gastritis in 2 of these 38 Of 25 without free acid in the secretion during fasting, only 6 had

delivering the stomach from the abdominal cavity to facilitate resection may at the same time increase gastric engorgement by hindering venous return The placing of large gauze packs may likewise obstruct venous return by compression of the regional veins By far the greatest cause of congestion is found in the actual procedure of resection. The usual technic calls for careful ligation of all blood vessels to the portion of the stomach to be resected beginning at or near the pylorus and proceeding toward the cardia The left gastric vessels are usually the last to be ligated after which a crushing or rubber-covered clamp is usually placed across the stomach at the level of the proposed resection The procedure has the effect of progressively converting the distal portion of the stomach into a closed vascular

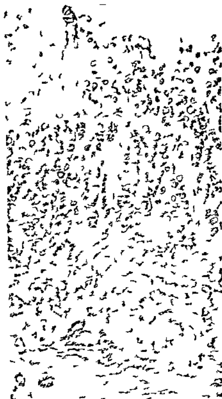


Fig 141 —Vascul co gestio plus hydrochlor ac d d t n tw h Ma ked erosion and superfi ial destruct n f mucosal ep thel m m c sal p ll es ha bee tapped by er e proce bt ed ert n ah wa th t hemoglob n f rythrocyte n thes essel h been hang d t acid h m ti X bo t 1 0

of 19 7 per cent Roentgen examination suggested gastritis in 9 of 42 cases of bleeding an incidence of 21 4 per cent

[We heartily concur with these observations in the light of our own experience —Ed]

Pseudogastritis of Operative Origin The incidence of gastritis reported from different climes and different countries varies widely Schindler and his co workers suggested that the gastritis observed was an artefact produced by the technic of gastric resection in the presence of *free hydrochloric* acid George B Sanders and Paul M Mecray[6] (Univ of Pennsylvania) found that when free acid was present in the stomach of the dog gastric changes were (1) *proportional to* the degree of gastric vascular engorgement which occurred during operation and (2) to the time elapsed between beginning the resection and the examination of the specimen The technic of gastrectomy as used in surgical clinics can reproduce these conditions The procedure of



Fig 340 —[illegible] [illegible] [illegible] d [illegible] and [illegible] nt du [illegible] [illegible] tw [illegible] M sal p thel um [illegible]

(6) Ann Surg 114 986-998 D c 1941

Hospital observation and treatment for one month are recommended (1) if the ulcer is acute and in a young patient (2) if it is less than 1 cm in diameter or (3) if it is on the lesser curvature or the anterior or posterior wall If healing is complete in one month, repeated observations should be made one month after discharge if it is not complete in one month on roentgenologic and gastroscopic examinations operation is advisable

Perhaps the strongest argument in favor of gastric resection for ulcer is found in an analysis of end results and mortality data Among 93 patients subjected to

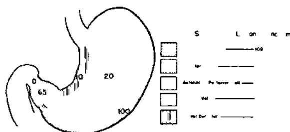


Fig 14 —Approximate [illegible] cancer in gastric ulcer [illegible]

gastrectomy for cancer the operative mortality was 25 per cent Including these operative deaths there were 20 per cent of five year cures In a small group in which end results were known 30 gastrectomies were performed under the diagnosis of benign ulcers all the ulcers proved to be cancer The operative mortality in this group was 10 per cent and including these deaths the five year rate of cure was 40 per cent Despite this small number of cases the likelihood of a lower mortality rate and a higher cure rate cannot be overlooked if the resection is done on the assumption that the lesion is an ulcer and not a cancer Thus the more benign the lesion appears the more likely the final cure The surgeon must remember the possibility of malignancy when carrying out gastrectomy for ulcer

sac into which the left gastric artery has been allowed to pump blood for 10 to 45 minutes depending on the speed of the surgeon and the actual technic used

Apparently gastroscopy rather than study of the surgically resected specimen should be the basis for evaluation of the frequency of the coexistence of peptic ulcer and gastritis

Gastric Ulcer and the significance of this diagnosis and its relationship to cancer are considered by Arthur W Allen and Claude E Welch[7] (Massachusetts Gen l Hosp) Gastric and duodenal ulcer have been discussed so frequently under the general heading of peptic ulcer that serious confusion has resulted regarding proper management of these two distinct entities Early symptoms in both diseases are much alike and the conservative measures found adequate in uncomplicated duodenal ulcer will also be temporarily effective for gastric ulcer The greater frequency of acute duodenal lesions compared with those in the stomach has enhanced the standardization of treatment of duodenal ulcer however this regimen applied to the more rare gastric ulcer has often proved disastrous

On the basis of a study of 277 patients with an original diagnosis of gastric ulcer of whom 39 finally were proved to have gastric cancer the authors conclude that gastric ulcer is fundamentally a surgical lesion in direct antithesis to duodenal ulcer Analysis of the 39 cases indicates that the gastric cancers which simulate gastric ulcer comprise an especially favorable group for cure On this basis alone surgery should be the treatment of choice in gastric ulcer (Fig 142) Immediate operation is recommended (1) if the ulcer is of short duration and the patient over 50 (2) if the ulcer is over 2 5 cm in diameter (3) if there is no free hydrochloric acid in the stomach (4) if the ulcer is in the greater curvature or in the prepyloric region or (5) if it is chronic and on the lesser curvature

(7) Ann Surg 114 498 509 October 1941

ders a major problem in military medicine The incidence of peptic ulcer in such disorders is high Consequently the policy of rejecting selectees known to have had an active ulcer within the past five years is wise and should be followed rigidly In questionable cases a detailed investigation should be made and the candidate accepted only if negative results are obtained When ulcers develop in the service or recur appropriate treatment must be given When the lesion is healed the patient may be discharged or may continue on limited duty in the continental United States He should not be allowed to return to full rations or active field duty

The relation of gastritis to military service requires clarification Clinical diagnosis of acute or chronic gastritis is vague indefinite and unsatisfactory Great care must be exercised in correlating symptoms with the mucosal changes seen gastroscopically Available evidence indicates that the so called simple nonspecific superficial atrophic and hypertrophic forms of chronic gastritis do not produce symptoms and hence do not constitute a cause of disability Ulcerative gastritis however may be associated with an ulcer like distress or with massive hemorrhage or both and seems at times at least to be related to the lesion peptic ulcer Patients with this condition should be included among those with ulcer and treated accordingly

[In this article the problem of peptic ulcer in wartime from the standpoint of diagnosis treatment and selection and disposition of draftees is adequately considered The author s attitude with reference to the controversial subject of gastritis is of special significance because of his close association with Schindler Whether or not we are in accord with his convictions in this respect they are worthy of our respectful consideration —Ed]

The Dyspeptic Soldier William Brockbank[1] presents a statistical survey on 931 consecutive patients with dyspepsia admitted to a military hospital during the first 18 months of the war They represented 8 5 per

(1) L t 1 394 J 10 1942

The operation carries no more risk if the omentum and the lymph nodes of the lesser curvature are included in the resection If this attitude is adopted in all ques tionable cases the cure rate will be even higher than 40 per cent in those cases with early malignant lesions

[This article and another by my colleague Waltman Walters (*Archives of Surgery* 44 370 March 1942) expressing a similar viewpoint are representative contributions to the current surgical literature on the therapy of gastric ulcer On the basis of actual repeatedly demonstrated pathologic fact the internist and surgeon see the diagnostic and therapeutic problem eye to eye under cer tain circumstances In other respects they may honestly differ as to therapeutic indications in the individual case if they remain loyal to their convictions Various factors enter into the de cision whether to treat or operate and fortunate is the patient in my judgment who is in a position to get the measured concurrent opinion of both internist and surgeon in the debatable case —Ed]

Peptic Ulcer and Irritable Colon in the Army Don ald T Chamberlin[8] (Lawson Gen l Hosp Atlanta, Ga) states that 316 patients were admitted to the gastro intestinal ection from Aug 1 1941 to May 1 1942 representing 9 per cent of the total hospital admissions and 18 per cent of admissions to the medical service Thirty one per cent had proved peptic ulcer These pa tients had had an average of 5½ months of army serv ice before symptoms became severe enough to require hospitalization Statistics from the Tilton General Hos pital Fort Dix N J are similar but show a higher incidence of peptic ulcer (49 out of 113 admissions)

Chamberlin believes that these statistics definitely indicate that the man with a peptic ulcer is unfit for military service No matter how well the man is before induction the break down in the Army is inevitable The chance that a patient with peptic ulcer may escape disabling symptoms in the service is slight He is an expense to the government and his induction or com mission is unwise

The Stomach and Military Service Walter Lincoln Palmer[9] (Univ of Chicago) considers digestive disor

(8) Am J Dig t Dis 9 245 48 August, 194
(9) J A M A 119 11 5 1159 Aug 8 194

returned to duty, mostly without any lowering of cate gory, the rest being discharged from the army Of all men discharged from the army through a particular command medical board during a particular period 14 2 per cent had peptic ulcer 54 per cent of these were discharged after less than 12 months service

There is no evidence of an increase in peptic ulcera tion as a result of the war but the war has revealed the unsuspected commonness of peptic ulcer and gas tritis in the civilian population before the war began It is necessary that the cause of the great increase in peptic ulceration since the last war should be de termined Every patient with dyspepsia of more than a month s standing should be examined clinically and roentgenographically If possible a fractional gastric analysis should be performed

Massive Gastric Hemorrhage Special Reference to Peptic Ulcer John V Bohrer (Knickerbocker Hosp New York City) reports that 40 825 patients were admitted from 1931 to 1940 of whom 456 had peptic ulcer Of the latter group 182 were admitted for gastric hemor rhage Of 80 classified as having massive gastric hemorrhage 14 died about 1 in every 3 100 All patients with gastric bleeding should be considered seriously ill and prescribed absolute rest in bed with sufficient morphine to combat fear and restlessness As soon as possible a Levine tube should be passed well into the stomach through the nostril for aspiration of liquid blood and lavage with saline solution until the stomach is free from blood clots If after the stomach is empty bright red blood continues to return through the tube the hemorrhage is still active and immediate operation is required

The therapeutic value of the Levine tube consists of the following factors Severe straining and reverse peristalsis of the stomach are inhibited by removal of the nauseating blood Feeding is easily accomplished

(2) A n. Surg 114 510 525 O t b 1941

cent of all admissions The monthly average throughout the period was 52 and was more or less constant Of these 397 were considered to have peptic ulcer This percentage fell in the successive six month periods, being 46, 44 and 33 per cent After the first two months of the war only 7 per cent of these patients were sent back to duty the remainder were discharged from the armed forces

The average figures obtained with this group agreed well with those of Allison and Thomas who reviewed 100 cases of dyspepsia in sailors and marines and demonstrated a gastric or duodenal ulcer roentgenographically in 45 per cent Several other figures have been published (see table)

PUBLISHED FINDINGS IN PATIENTS ADMITTED TO SERVICE HOSPITALS IN THE PRESENT WAR

AUTHORS	TYPE OF HOSPITAL	TOTAL PATIENTS	ULCERS %	NO OF GASTRIC ULCERS	NO OF DUODENAL ULCERS	% OF ULCERS DUODENAL
Allison and Thomas	Naval	100	45	6	34	85
Brockbank*	Military	931	42 5	52	275	84
Graham and Kerr	Military	246	64	23	135	85
Maingot	General	256	56	15	128	89
Morris	Military	[illegible]00	50			
Payne and Newman	E M S	287	89	42	164	80
Spillane	Military	over 200	32	10	54	84
Willcox	E.M S	41	69	7	19	73

* Includes [illegible] cases of carcinoma and [illegible] of gastro-enterostomy in which there was no [illegible] evidence of the site of the ulcer

Of the total patients with ulcer 13 3 per cent had gastric, 15 3 per cent pyloric and 71 4 per cent duodenal ulcers most of these gave a history of many years duration A group of 534 were considered to have no peptic ulceration 90 per cent of these were

aid materially in an uneventful convalescence Early operation before repeated exsanguination occurs is essential for a lowered mortality rate Use of chemotherapy either preoperatively or as a massive dose intraperitoneally at the end of operation may still further reduce the mortality especially in patients over 45 with duodenal ulcers since pneumonia seems to be a complication causing many of the deaths

Alimentary Azotemia and the Bleeding Peptic Ulcer Syndrome C Frank Chunn Henry N Harkins and R T Boals[3] (Henry Ford Hosp) state that azotemia occurs in cases of massive hemorrhage into the upper intestinal tract as in bleeding peptic ulcer The degree of azotemia is of considerable prognostic significance high blood urea nitrogen values are associated with a high mortality rate Persistent azotemia tends to indicate persistent bleeding in most instances rather than serious hepatic or renal damage and therapeutic indications are calculated accordingly In cases of hematemesis and melena azotemia is essentially caused by absorption of the red cells rather than of the plasma fraction of the lost blood This is accounted for by the high protein content of the cell hemoglobin Experiments conducted by the authors show that starvation dehydration bleeding anemia and shock do not play a major part in production of azotemia Presence of the liver with an intact portal circulation is essential for occurrence of alimentary azotemia

The authors propose the term alimentary azotemia for the syndrome of increased blood urea nitrogen following alimentary absorption of large amounts of digested protein In bleeding peptic ulcer a large share of the resultant azotemia is probably alimentary azotemia caused by ingestion of blood proteins part of it may be due to other types of extrarenal azotemia while in some instances actual renal azotemia may be a contributory factor

(3) A h Surg 43 773 788 No emb 1941

The blood clot in the vessel is not mechanically removed by vomiting peristalsis or pangs of hunger If lavage removes a friable clot it is evidence of a useless clot that will not stop bleeding The ferments first removed with the blood by lavage are now combined with food and do not digest the ulcer vessel or clot The Andresen diet answers this requirement perfectly Administration of adrenalin or various coagulants through the tube may be of value in diffuse bleeding from gastritis but is of little value in the presence of an open vessel

If continued bleeding is indicated by the syndrome of rapid pulse decreased blood pressure air hunger slight delirium and reduced blood count and hemoglobin content a transfusion sufficient to raise the blood count and hemoglobin a measurable amount should be given If after transfusion the red cells and hemoglobin show a marked decrease in 1 to 12 hours bleeding is taking place from an eroded vessel and immediate operation is indicated Undiluted blood fresh containing a normal concentration of prothrombin red cells with normal intracellular potassium normal white cells and platelets seems to be preferable to fresh citrated or banked blood especially in patients near exsanguination

Analysis of the patients treated by various procedures indicated that gastrectomy is the operation of choice both for control of hemorrhage and for ultimate cure Bleeding following gastrectomy in surviving patients was not observed Gastrectomy is often more difficult to accomplish in cases of duodenal than in cases of gastric ulcer Local excision of a gastric ulcer combined with gastro enterostomy apparently gives satisfactory results If ligation of a vessel or plication of the ulcer only is accomplished nonabsorbable suture material should be used however bleeding has recurred following this procedure Gastro enterostomy per se is of no value to stop immediate bleeding or to prevent recurrence Vitamins, particularly B and C given preferably by hypodermic in the postoperative period will

and physical examination The source was found to be a faulty can opener which caused small sharp edged pieces of tin to fall into the food of an opened can One patient had such severe hemorrhages by bowel that he went into almost complete circulatory collapse Treatment consisted of bed rest and for the patient *with severe hemorrhages soft diet and blood trans fusion.*

When the apparent cause was discovered the entire crew was given large quantities of thick oatmeal mush and strong tea as prophylactic measure the mush to gather up the pieces of metal in the intestines and the strong tea for the astringent action on the intestinal mucosa This measure plus replacement of the can opener apparently effected the cure since no new cases have developed and the original patients have remained well

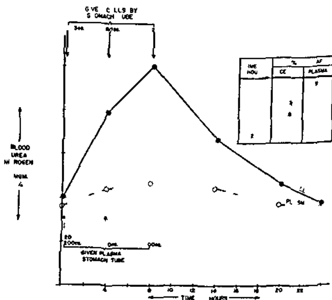
[Hill s observations probably are correct In single isolated cases the underlying cause under such circumstances would have been difficult of solution.—Ed]

Prognostic Significance of Blood Urea Nitrogen Fol lowing Hematemesis or Melena Leon Schiff Richard Stevens Harold K Moss and Ellen S Garber[5] (Univ of Cincinnati) observed 119 patients who were treated with a modified Meulengracht diet Determinations of the urea nitrogen were mostly carried out in duplicate on oxalated whole blood by the aeration method of Van Slyke and Cullen The first specimens were obtained immediately after admission before administration of food or fluid Later specimens were generally obtained under fasting conditions although in some cases the blood was obtained shortly after a meal usually break fast

The distribution of the probable causes of hemor rhage in this series is given in Figure 144 Diagnosis was based on clinical x ray and gastroscopic examina tions and in 32 cases on observations at operation or

(5) Am J Dg t. D 9 110 113 M h. 1942

[Investigations of a clinical and experimen al nature concerned with the pathogenesis of alimentary azotemia (extrarenal uremia) have figured largely in the gastro enterologic literature of the pa.t few years There is a difference of opinion as to the mechanism and prognostic significance of this condition Most observers are agreed that the height to which blood urea rises is of value in judging the severity of the hemorrhage and that the azotemia is



F g 143 —Comp au e effe ts f blood lls nd blood plasma in product o of al m nt y az tem dogs.

accounted for mainly by absorption of nitrogen from the blood in the bowel A critical review of the subject stressing other less frequently considered factors in the mechanism of this disorder has recently been made by Black (*Quarterly Journal of Medicine* 11 77 April, 1942) Those directly interested will be repaid for reading it —Ed]

***Hemorrhage*, Traumatic, Intestinal Tract U S A Spica** R V Hill[4] (M C, U S N) reports four cases occurring within six days The disease was character ized by sudden onset of dizziness weakness and col lapse without apparent reason on the basis of history

(4) U S Nav M, B ll 40 74 745 July 1942

proved fatal the already elevated blood urea nitrogen generally continued to rise or fluctuated above normal limits instead of reaching a maximum concentration in 24 to 48 hours and then dropping to normal on the third or fourth day as in patients with a single non fatal hemorrhage

The authors conclude that a blood urea nitrogen concentration of less than 30 mg per cent in patients with hematemesis due to peptic ulcer hepatic cirrhosis or undetermined cause is a favorable prognostic sign The presence of a blood urea nitrogen content of 50 mg per cent or more following hematemesis or melena is accompanied by a fatal outcome in one third of cases An elevation of 70 mg per cent or more is accompanied by a fatal outcome in about two thirds of

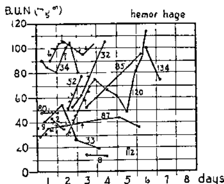


Fig 145—Bl d u nt gen d t mnt n f tal of h m tem d melen

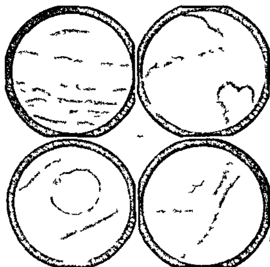
cases Elevation of the blood urea nitrogen is particularly ominous following hematemesis in patients with hepatic cirrhosis Shock increases the mortality rate in patients with azotemia following hematemesis or melena In the presence of a single hemorrhage a blood urea nitrogen curve which reaches its maximum in 24 to 48 hours and then drops to normal on the third or fourth day is almost always a favorable prognostic sign In the presence of repeated hemorrhage a blood urea nitrogen curve which continues to rise or remains abnormally elevated is usually associated with a fatal outcome

autopsy Ulcers included gastric duodenal and anastomotic lesions and were in every case demonstrated by x ray examination gastroscopy operation or autopsy Gastritis was considered the source of bleeding only when a definite erosion was demonstrable The largeness of the group of cases with bleeding of undetermined origin may be explained by the frequency of negative x ray findings and the absence of erosions on gastroscopic examination which was usually carried out 10 days to 2 weeks after hemorrhage The miscellaneous group included two cases of ruptured aortic aneurysm and one each of gastric neurinoma duodenal carcinoma pancreatic carcinoma esophagitis and thrombocytopenic purpura

Fig 144 —Probable [illegible] of hemorrhage in 135 patients with hematemesis or melena

The blood urea nitrogen was elevated to 30 mg per cent or more in about two thirds and to 50 mg per cent or more in about one fifth of the cases In no instance of hematemesis due to peptic ulcer hepatic cirrhosis gastritis carcinoma or undetermined cause did death occur as the result of hemorrhage in the absence of an increased blood urea nitrogen content In the presence of azotemia [illegible] of 8 patients with hepatic cirrhosis died as did 7 of 35 patients with peptic ulcer (including one who died of perforation) In the presence of azotemia shock increased the mortality rate in patients with hematemesis or melena The mean maximum blood urea nitrogen was higher in patients 50 years or over than in those below this age limit In patients with repeated or continued hemorrhages which

base are more characteristic of a syphilitic ulcer The appearance is suggestive of the phagedenic ulcers of the leg and not unlike ulcers of tertiary syphilis seen in the palate This lack of normal red color seems explainable in that the basic pathology underlying the ulcer is that of an obliterative vasculitis The infiltrating lesions of syphilis producing large tumors of the stomach are most difficult to differentiate gastroscopically from similar



F g 146 (top l ft) —N rm l st m h mu g tr op ally
F g 147 (top ght) —Mult pl yphil t g t ul
F g 148 (bott m l ft) —R und ul f syphil f t m h
F g 149 (b tt m ght) —Syphil t tum f t m h

lesions of other etiology The prominence of superficial blood vessels on the borders of the tumor with pallor of the mucosa due to fibrosis or to mucosal atrophy or to pressure from beneath (Fig 149) are differential points The diffusely infiltrating type is suggestive of a syphilitic lesion when there is a flattened thickened appearance of the rugae while the stomach wall is flexible

Gastric Hemorrhage with Hereditary Pseudohemophilia Gastro intestinal hemorrhage as well as hemorrhage in other parts of the body may occur in conjunction with this condition It is uncommon to find a blood dyscrasia as the primary etiologic factor in gastro intestinal hemorrhage Gastritis as the cause of gastric bleeding is being recognized more and more frequently L A Smith and C H Watkins[6] report a case with a combination of these two conditions

Gastroscopic Diagnosis of Syphilis of the Stomach Cecil O Patterson, Milford O Rouse and John S Bagwell[7] (Baylor Univ) summarize the gastroscopic findings in 12 patients who presented clinical data suggestive of syphilis of the stomach Symptoms referable to the stomach had lasted from three months to two years In order of frequency, they were burning epigastric pain with or without relief on ingestion of food nausea vomiting cachexia hematemesis and palpable mass Age incidence was 24 65 years All patients had positive serologic reactions for syphilis and absence of free gastric acid With one exception there was roentgen demonstration of a filling defect either an ulceration, tumefaction prepyloric narrowing or diffuse thickening of the stomach Two gastro enterostomies and one resection provided specimens showing gross and microscopic changes similar to those described in gastric syphilis

As seen gastroscopically these lesions were of three morphologic types (1) single or multiple ulcerations of the gastric mucosa in six cases (Figs 147 and 148) (2) nonulcerating tumors of the stomach in three cases (Fig 149), and (3) flattened or thickened appearance of the rugae evidencing local or diffuse, subacute or chronic infiltration of the stomach in three cases (Figs 150 and 151) Although it might be difficult to differentiate the less common round syphilitic ulcer from the peptic ulcer the purplish red sloping edges with a dirty gray

(6) Proc. Staff Meet May Cl 16 589 591 Sept. 10 1941
(7) South. M J 35 655 0 June, 1942

early carcinomatous ulcers are attributed respectively to the effect of such treatment on secondary peptic ulceration of cancerous tissue and to the filling in of the base of the ulcer with the latter The rate and extent of healing of an ulcerous gastric lesion undergoing adequate treatment are of primary importance in differential diagnosis However all treated patients should have periodic reexamination irrespective of how favorable the response Such follow up is particularly imperative under the following circumstances location of the lesion in the prepyloric first inch or on the greater curvature large size consistent achlorhydria persistent or frequent recurrence of occult blood in the feces during treatment late onset in an elderly patient and reduced gastric acidity and secretory volume estimated under basal conditions

Diagnosis of Gastric Cancer Analysis of Gastroscopic and Roentgenologic Findings Frederic E Templeton and Richard C Boyer[9] (Univ of Chicago) analyze 189 cases in which both gastroscopic and roentgen examinations were done The material included all the polypoid ulcerating and infiltrating cancers and also the benign counterparts namely polyps ulcers and certain forms of gastritis In 74 cases the character of the lesions was proved microscopically in surgical specimens Most of the other cases were followed sufficiently long so that their true nature seemed assured

The roentgenologic demonstration of a gastric mucosa normal in every respect excludes gastric neoplasm However it is not always possible by x ray examination alone to explore every square inch of the mucosa in some patients the limitations are considerable Gastroscopy therefore is a companion method desirable and essential in patients whose stomachs cannot be adequately examined roentgenologically Two patients in whom cancer was not found by the roentgenologists because of inadequate examination were easily examined by the gastro-

(9) Am J R tg 1 4 6 74 F b y 194

This is different from the usual appearance of the malig nant infiltration and from the appearance of the non specific form of gastritis The tendency for narrowing

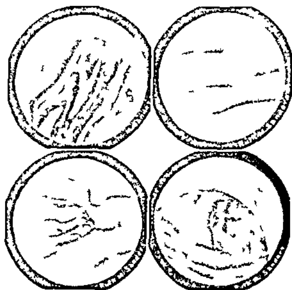


Fig 1 0 (t p left) —Syph lit c h morrhagic ga t tis, lower third of t m h
Fig 151 (t p right) —Syphil t leathe bottle stom h mucosa.
F g 15 (bottom left) —Gast ce
F g 153 (bott m ght) —M l g nt ulce low thi d f stomach le at d ma g s and nod les f t s o in ul er ba

of the antrum in the diffuse fibrosis of gastric syphilis has been long recognized and was observed gastroscopi cally in one case of the present series

Carcinomatous Gastric Ulcer George B Eusterman[8] (Mayo Clinic) states that small ulcerating forms of gastric *carcinoma not only may be clinically indistin* guishable at times from chronic benign ulcer but may respond to medical treatment so favorably as to give a wrong impression of their true nature Such response seems especially characteristic of carcinoma in situ The real and apparent favorable reactions to treatment of

(8) J A M A. 118 1 J n 3 194

early carcinomatous ulcers are attributed respectively to the effect of such treatment on secondary peptic ulceration of cancerous tissue and to the filling in of the base of the ulcer with the latter The rate and extent of healing of an ulcerous gastric lesion undergoing adequate treatment are of primary importance in differential diagnosis However all treated patients should have periodic reexamination irrespective of how favorable the response Such follow up is particularly imperative under the following circumstances location of the lesion in the prepyloric first inch or on the greater curvature large size consistent achlorhydria persistent or frequent recurrence of occult blood in the feces during treatment late onset in an elderly patient and reduced gastric acidity and secretory volume estimated under basal conditions

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(9) Am. J Ro tg n l 47 6 4 F b ry 194

scopists and cancer was found In two other patients distorted rugal patterns on films raised suspicion of a lesion but a definite diagnosis was not made, since nothing abnormal was seen at roentgenoscopy In one patient the gastroscopists failed and in the other succeeded

TABLE 1 —SUMMARY OF 45 CASES IN WHICH INFILTRATING LESIONS WERE IDENTIFIED BY GASTROSCOPIST OR ROENTGENOLOGIST OR BOTH

MEANS OF IDENTIFICATION	No OF LESIONS		
	Chronic Gastritis Necessitating Differentiation from Neoplasm	Lymphosarcoma	Carcinoma
Gastroscopy and roentgenology	4	2	25
Roentgenology			5
Gastroscopy	{4 {1		1
Neither gastroscopy nor roentgenology			1
Gastroscopy and roentgenology not confirmed at exploratory laparotomy	1	Benign polyp 1	

Cases not proved by pathologic examination

TABLE 2 —SUMMARY OF 28 PATHOLOGICALLY PROVED ULCERS IN WHICH DIFFERENTIATION FROM BENIGN OR MALIGNANT LESION WAS ATTEMPTED BY GASTROSCOPIST OR ROENTGENOLOGIST OR BOTH AT FIRST EXAMINATION

MEANS OF ESTABLISHING THE CORRECT DIAGNOSIS	No OF LESIONS	
	Benign	Malignant
Gastroscopy and roentgenology	2	12
Gastroscopy	5	2
Roentgenology		3
Neither gastroscopy nor roentgenology		4

in confirming the presence of cancer Likewise cancer suspected at gastroscopy should be confirmed by x ray examination In six patients the gastroscopists considered the possibility of cancer not found at adequate

roentgenologic examination In one patient cancer was confirmed and in one not confirmed by pathologic studies In four patients the gastroscopist could not confirm his findings at subsequent examinations In two laparotomy followed diagnosis of cancer by both methods In each instance the stomach felt normal but the mucosa was not inspected and biopsy was not made One patient showed a benign polyp at autopsy The other patient is still living and does not appear to have cancer

In the differentiation between polypoid and infiltrating lesions one method proved to be no more and no less accurate than the other Lesions in which the gastroscopist at first examination suspected cancer not confirmed by x ray examination or by gastroscopy at subsequent examinations were explained by the gastroscopist on the basis of a chronic gastritis A combination of gastroscopy and roentgenology will result in a higher percentage of correct diagnoses than will the use of either procedure alone

Differential Diagnosis and Treatment of Acute Abdominal Injuries Charles F Rea[1] (Univ of Minnesota) states that in all acute abdominal injuries two factors influence the surgeon in the choice of a surgical or conservative way of treatment (1) whether the trauma is blunt or penetrating and (2) whether a solid or a hollow organ is injured Nearly all penetrating wounds and certainly all perforations of hollow viscera should be operated on as soon as the condition of the patient permits To determine whether a hollow or a solid organ has been injured history location of the trauma and clinical findings are of prime importance Patients who complain of abdominal pain rigidity and tenderness require x ray examination (an upright film) of the abdomen to rule out free intraperitoneal gas If no free gas is seen an open perforation of the stomach and colon is not present If the pain is in the lower quadrant a cystogram should be made to rule out tear of the bladder

(1) Am. J S g 7 316 3 0 A gu t 194

If both cystogram and upright film are negative and if the possibility of rupture of the liver spleen or kidney is ruled out an exploratory operation is required to determine the possibility of a tear in the small bowel

Injuries to solid viscus are best treated conservatively as long as the patient shows no signs of shock While the mortality of penetrating wounds to the abdomen is about 50 per cent the results following surgery are far superior to those following nonintervention

Alkalosis Complicating Sippy Treatment of Peptic Ulcer *Joseph B Kirsner and Walter Lincoln Palmer* (Univ of Chicago) analyze 135 episodes of alkalosis observed during alkali treatment of peptic ulcer in 111 patients Multiple episodes of alkalosis occurred in 18 patients The disturbance was slight in 71 moderate in 27 and severe in 37 The electrolyte balance was undisturbed during subsequent alkali therapy in 29 persons recovered from a previous episode The alkalosis was not a direct function of the quantity of alkali received Symptoms usually appeared within 4 to 10 days after beginning treatment and consisted of a distaste for milk and cream weakness dizziness headache dryness of the mouth nausea and vomiting Some patients did *not complain of any discomfort There was no constant* relation between severity of symptoms and degree of chemical alkalosis

Bleeding occurred in 60 of the 135 episodes There seemed to be no correlation between severity of bleeding and frequency of alkalosis Gastric retention was present in 6 of 71 patients with slight alkalosis in 10 of 27 with moderate alkalosis and in 20 of 37 with severe alkalosis Disease of the genito urinary tract was present in 16 patients Urea clearance was normal in three and reduced or low in six Acid base balance was undisturbed in 23 patients with renal disease similarly treated in 10 of whom renal function at onset of treatment had been normal and in 6 of whom it had been low Hyper

(2) Arch. I t. Med 69 89 80 May 1942

tension was present in 37 of the total group Urea clearance previously had been normal in 7 and low in 14 of this group Alkalosis did not occur in 17 hyper tensive patients with ulcer similarly treated in 7 of whom renal function at onset of treatment had been normal and in 8 of whom it had been low

Effect of alkalosis on urea clearance was studied in 48 patients Renal function at onset of alkali therapy was normal in 24 and reduced or low in 24 Urea clearance during alkalosis did not change in 20 in 14 of whom normal values had been obtained originally Renal func tion diminished in 28 it had previously been normal in 10 and low in 18 The depression of urea clearance during alkalosis depended apparently on severity of alkalosis and preexistent impairment of renal function Urea clearance was determined within several weeks after alkalosis in 22 of the 28 Return to previous level was noted in 19 the original value had been normal in 6 of these and low in 13 Failure to return to previous levels was observed in three patients the original values had been normal in two and low in one later it re turned to the original level in all three

Blood urea nitrogen was elevated during alkalosis in 55 Hypertension was present in 16 of these massive hemorrhage in 16 and gastric retention in 25 Albumin and casts were detected in the urine during alkalosis in 28 Gross or microscopic hematuria was not seen

It was not necessary to discontinue alkali for or to administer additional chloride to 51 patients Treat ment of the remaining patients consisted variously of change of antacid administration of either ammonium or sodium chloride with or without discontinuance of alkali and parenteral use of fluid Clinical improvement rapidly followed therapy

The effect of prolonged alkali therapy on renal func tion was studied in 62 patients divided into two groups those whose condition was uncomplicated by alkalosis and those in whom alkalosis developed There were 29

patients in the former Urea clearance decreased in only one of this group diminishing from 67 to 40 per cent in a woman 68 after ingestion of large quantities of alkali for 5½ years Blood pressure, value for blood urea nitrogen and urine remained normal In the latter group there were 33 with alkalosis on 48 occasions Decrease in urea clearance was noted in only two, both patients with hypertension

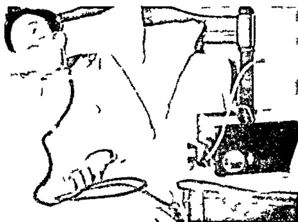
[Apart from the intrinsic merit of the research reported in this article is the significant bibliography on the subject presented for the convenience of future workers in this field It should be pointed out that in the absence of high grade refractory pyloric obstruction or renal disease alkalosis can readily be avoided by the use of newer and safer antacids with which the profession is now familiar When necessary minimal doses of magnesium, soda and calcium carbonate especially the first mentioned can be given as adjuvants with more or less impunity in the average case —Ed]

Problems Encountered in Use of Aluminum Hydroxide Gel by Nasogastric Drip in Treatment of Peptic Ulcer George H Drumheller[3] (Univ of Pittsburgh) describes a new type of nasogastric drip which delivers a set amount without disturbing the system and uses no valves This is particularly advantageous in hospital work, because corrosion and clogging are prevented The rubber tube may be sterilized before using and discarded after use, eliminating other maintenance For accurate adjustment an electrical time delay relay was developed, which allows the pump to deliver a single stroke (5 drops) and then stops the pump for a time This 'wait' can be adjusted from less than a second to more than 60 seconds depending on the dial setting before making another stroke A special aluminum hydroxide gel was developed to prevent sedimentation and thickening This new substance has the consistency of milk of magnesia Two drops of oil of peppermint is added to 128 fl oz. of the gel Thickening on heating can be prevented by adding 10 gr sorbitol per fluidounce glycerin will do the same thing Either of these additions seems not

(3) Am. J Dig est. Dis 8 443 446 Dec mbe 1941

only to improve the taste but also adds to the stability

The patient must be convinced that he will benefit tremendously by the treatment in order to prevent intentional removal of the tube Generally if the drip is set for 7 drops a minute for the first 24 hours the patient will tolerate the medication well and vomiting is often avoided The drip is then set for 15 drops a minute for the remaining treatment with an increase to 20 drops



F g 154 —M h p n pump in p t

per minute through the nights Good nursing care is imperative simplification of the apparatus permits even a probation nurse to understand its operation The nursing staff must understand that the treatment has to be continuous even during the night To combat constipation fecal impaction and intestinal obstruction vitamin B_1 lubricants and enemas are effective Drumheller prefers the use of a nylon obturator to rubber because the nylon is unaffected by weak acids or alkalis and is not digestible a tube of this material does not kink is easily reinserted at any time during treatment and does not soften

Treatment of Peptic Ulcer without Alkalis George F Dick and C Wesley Eisele[4] (Univ of Chicago) present a study of 41 patients with peptic ulcers who were selected on the basis that their x ray studies before treatment showed definite ulcer craters and that subsequent studies were made at sufficiently fre quent intervals to indicate the course of the crater The pa tients were given 1 4 oz of a mix ture of equal parts of milk and cream at hourly intervals during the day and often during the early evening In some cases milk alone was given When all distress was relieved, small amounts of bland foods were added gradually Added vitamins were given in most cases Physical and mental rest was emphasized Atropine was given in some cases In eight cases a few single doses of alkali were given to control pain Foci of infection were re moved when present Therapeutic aspiration of the stom ach at bedtime was not done Instead one or more bed time aspirations were done when treatment was begun

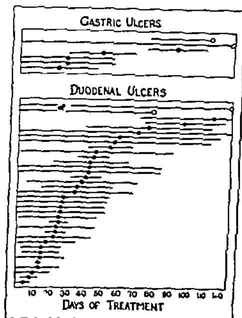


Fig 155 —Time of r y c te app ran e Each case i p ented by a bar left end of wh ch d te t me f l t x y e minat on whi h showed at ght d di ates fir t x min t n at whi h c at had d ppe d m dpo t f bar (d t) most p ob ble time of al d sai pe a e r l at ght d m that cr te w st ll y sent t la t e mi t o

(4) J A M A 118 38 41 J 3 194

and in patients showing residuum the quantity of milk and cream per hour was reduced until the stomach was practically empty at bedtime Seven patients had gastric ulcers and 34 duodenal ulcers Two of the latter group were followed through two distinct attacks thus making 36 duodenal ulcers in the series Twenty six of the patients were men Ages ranged from 23 to 74 years Five patients were entirely ambulatory and 36 were hospitalized from 3 to 52 days

The time of disappearance of the crater in each case is represented by a bar in Figure 155 The left end of the bar indicates the time (days of treatment) of the last x ray examination at which a crater was demonstrated and the right end the time of the first examination at which the crater was shown to have disappeared In 25 cases the last demonstration of the crater was at the initial examination In 17 cases an average of 76 days elapsed between these two pertinent examinations Unfortunately this introduced a considerable latitude as to the actual time of crater disappearance The midpoint of each bar indicated by a dot represents the most probable time of disappearance (the mean time of crater disappearance)

The craters in 86 per cent of the group of duodenal ulcers had disappeared within 75 days (mean time of crater disappearance) and those in 70 per cent of the cases were actually demonstrated to have disappeared within 75 days In two cases the craters did not disappear completely although they decreased considerably One of the patients was symptomatically well and apparently in good health after the first week of treatment In the second case a duodenal ulcer crater disappeared promptly without use of alkalis one year before but in the attack under consideration the crater persisted for 75 days although it became shallow with indistinct margins thus showing definite evidence of healing Subsequently the crater disappeared with administration of alkalis The gastric ulcers followed in general a similar

course Complete relief of symptoms occurred in nearly all cases of both groups long before the crater disappeared In 31 cases all symptoms were controlled within one week In nine cases the progress notes concerning relief from pain were inadequate The benzidine reaction of the stools was negative in 14 cases despite presence of a crater In 12 cases a positive test became negative before the x ray examination which first showed the disappearance of the crater In one case a positive benzidine test persisted after the crater had disappeared

These data demonstrate that healing of peptic ulcers will progress satisfactorily without the attempted neutralization of gastric acidity with alkali. Speed of recovery compares favorably with that under any other type of treatment

DISEASES OF THE BILIARY TRACT AND PANCREATIC SYSTEM

Sphincter Mechanism of the Common Bile Duct in Human Subjects George S Bergh[5] (Univ of Minnesota) discusses its relation to certain types of stimulation A distinct sphincter of the common bile duct has been demonstrated, and physiologic studies have indicated that it can function independently of the intestinal musculature Duodenal motility and tone may possibly influence the resistance to bile flow In man the anatomic arrangement of the window in the duodenal muscle through which the bile duct enters the intestine is such that duodenal peristalsis probably exerts a minimal effect Functions attributed to the sphincter of Oddi are (1) making possible the filling of the gallbladder (2) preventing the regurgitation of intestinal contents into the bile duct (3) regulating the discharge of bile into the duodenum and (4) erecting the papilla The discharge of bile into the duodenum is dependent on the

(5) Surgery 11 299 330 February 1942

tonus of the sphincter activity of gallbladder and pressure of bile secretion To secure information concerning the effect of various types of stimulation on the sphincter mechanism the resistance to the flow of fluid may be studied in patients with intubation of the common bile duct

Since there is no method allowing measurement of the sphincter resistance in entirely normal human subjects Bergh has considered the figures obtained for patients who had recovered from their operations who were feeling well and who had fasted for six to eight hours as normal In such cases the sphincter withstands pressures between 9 and 23 cm water and usually the resistance is around 12 to 15 cm water Changes of a few millimeters in the intraductal pressure occur during respiration and marked changes occur during coughing laughing or vomiting because of temporary increase in intra abdominal pressure Even with stabilization of the sphincter resistance changes of several centimeters may occur spontaneously from time to time In some patients the sphincter remains irritable for weeks after removal of a calculus from the common bile duct the muscle readily goes into spasm After prolonged external drainage of the duct the irritability usually disappears and the sphincter returns to normal Ingestion of a fatty meal consisting of egg yolks and cream causes relaxation of the sphincter proteins occasionally produce relaxation but neither a carbohydrate meal nor glucose given intravenously has any significant effect Water orally also fails to produce a change Morphine codeine pantopon and dilaudid cause contraction of the sphincter of Oddi Amyl nitrite and nitroglycerin produce relaxation of the sphincter but atropine does not Erythrol tetranitrate is ineffective Trasentin epinephrine ephedrine histamine and ethyl alcohol sometimes produce sphincter relaxation but the effects are variable

Magnesium sulfate may produce relaxation with or without an initial contraction it may produce an initial

contraction followed by a return to the original tonus level or there may be no effect Relaxation, when it does occur usually is not great and contraction of the gall bladder following administration of magnesium sulfate probably is more important than sphincter relaxation in producing a flow of bile into the duodenum in patients with a functioning gallbladder Atropine, pilocarpine papaverine posterior pituitary extract benzedrine, pros *tigmine caffeine sodium benzoate and theophylline ethyl* enediamine have no significant effect on the sphincter The effects of sodium dehydrocholate histamine, epinephrine ephedrine calcium gluconate and calcium chloride are not constant Severance of the nerves in the hepato-duodenal ligament is not recommended as a means of lowering sphincter resistance

Applied Physiology of Bile Secretion and Bile Salt Therapy A C Ivy[6] (Northwestern Univ) attempted to answer questions concerning the regulation of bile salt output and the rational therapeutic use of bile salts in hepatic and biliary tract diseases by experiments with animals The results showed that protein promotes the formation of bile and cholic acid in the dog a fact worthy of consideration in management of cholecystectomized patients Bile salt output is maintained at a relatively constant level because the rate of production is balanced by the rate of destruction The rate of production depends primarily on the amount of protein metabolized and the rate of destruction on the rate of enterohepatic circulation of a particular quantity of cholic acid About 10 per cent of a quantity of cholic acid is lost during each enterohepatic circuit Excessive bile salt causes catharsis which increases the loss Given a high protein diet and otherwise normal conditions a cholecystectomized subject probably should pass a larger volume of bile through the common duct than a subject with a normal gallbladder

Oxidized cholic acid (dehydrocholic or triketocholanic

(6) J A M A 117 1151 11 4 O t 4 19[illegible]

acid) is a hydrocholeretic agent The bile formed is less viscous and contains less total solids per cubic centimeter than the bile formed in response to glycocholic and taurocholic acid Sodium dehydrocholate consistently increases the rate of blood flow through the hepatic artery This is not true of sodium cholate glycocholate and taurocholate Evidence showing that daily administration of bile salts in the presence of complete obstruction of the common bile duct is harmful and that administration of sodium dehydrocholate speeds the rate of recovery from obstructive jaundice after release of the obstruction was not obtained Production of choleresis obviously flushes the bile ducts but not the gallbladder However in the presence of normal formation of bile frequent evacuation of the gallbladder facilitates and speeds the removal of sediment from the viscus

Duodenal Intubation A Fidler James Innes and L S P Davidson[7] (Edinburgh Univ) discuss the significance of the cellular contents of bile in the diagnosis of biliary tract diseases They studied the cellular content of (1) bile removed by duodenal intubation after administration of magnesium sulfate peptone and olive oil to patients with and without biliary tract disease (2) bile aspirated at operation from the gallbladder and common duct of patients with cholecystitis and cholelithiasis and (3) fluid removed from the mucosa of the human stomach duodenum jejunum and ileum exposed at operation which had been submitted to the local effect of saline peptone and magnesium sulfate

In all cases an attempt was made to establish the nature of the cells in the bile In fresh preparations most of them appeared to be round cells (Fig 1?6) and only a small number were recognizable as columnar epithelial cells The round cells were about the size of leukocytes and in the beginning were considered leukocytes This first impression received support from examination of the deposit stained with methylene blue

(7) B t M J 865 869 D 0 1941

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Oxidized cholic acid (dehydrocholic or triketocholanic

(6) J A M A 117 1151 1154 Oct 4 1941

bation before administration of biliary stimulants contained a negligible number of cells Bile removed from normal persons after administration of magnesium sulfate usually contained many cells, that removed from the same persons after administration of peptone or olive oil contained a negligible number of cells Bile removed



Fig 157 (left) —Sam ll p d g t d with L hm n s mu l t g p lym ph l k yt × 300
Fig 158 (ht) —H gh p w ph tom g ph f m ll h w th t ll wh h pp to b p lym rph l uk cyt p th l l lls with di nt gr t g l × 750

by duodenal intubation from patients with chronic cholecystitis and cholelithiasis following administration of magnesium sulfate usually contained many cells whereas after the use of other biliary stimulants cells were absent or scanty furthermore bile aspirated from the gallbladder and common bile duct of the same patients at subsequent operation contained a negligible number of cells The conclusion to be drawn from the experiments is that bile removed by duodenal intubation following administration through the tube of 30 cc of a 33 per cent solution of magnesium sulfate may contain

neutral red and Leishman's method, as many of the nuclei appeared to be lobulated The stained preparations were however far from satisfactory and the cells were therefore removed from the influence of bile digestive juices and hypertonic magnesium sulfate solution by washing the flocculi immediately in saline and then suspending them in serum The improvement in staining effects showed the cells to be mostly cuboidal epithelial cells whose cytoplasm had largely disappeared and whose nuclear chromatin was rapidly undergoing degenerative changes (Figs 157 and 158) Examination under the oil immersion lens clearly revealed the difference between the detached broken up portions of nuclear chromatin and the lobulated nucleus of a leukocyte Bile stained cells were noted in about 40 per cent of the cases The occurrence of fatty acids and salts in the deposit of bile obtained after administration of olive oil must be remembered, because they may be mistaken for cellular elements



Fig 156 —W t p epa tion of ell in fl cul in bile obta ned by dq d nal dra n ge ft r u e f 30 cc 33 per cent m gnes um sulfate × 400

Bile removed from normal persons by

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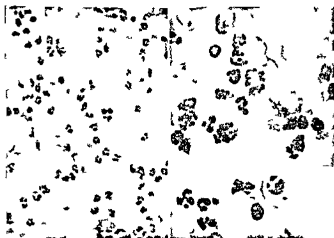


Fig 157 (l ft) —S m ll p d g st d w th L hm n mu l t g p lym ph l k yt × 300
F g 158 (ght) —H gh p w ph t m gr ph f m ll h ws th t ll wh h pp t be p lym rph l k cyt p th l l ll w th di nt g t g u l × 50

by duodenal intubation from patients with chronic cholecystitis and cholelithiasis following administration of magnesium sulfate usually contained many cells whereas after the use of other biliary stimulants cells were absent or scanty furthermore bile aspirated from the gallbladder and common bile duct of the same patients at subsequent operation contained a negligible number of cells The conclusion to be drawn from the experiments is that bile removed by duodenal intubation following administration through the tube of 30 cc of a 33 per cent solution of magnesium sulfate may contain

large numbers of cells produced by the local irritation of this concentrated solution on the duodenal mucous membrane this does not necessarily indicate preexisting inflammatory disease of the biliary tract

Reflexes Originating in the Common Duct Giving Rise to Pain Simulating Angina Pectoris Two such cases are reported by I S Ravdin H P Royster and George B Sanders[8] (Univ of Pennsylvania) One is described here

Woman 45 complained of recurrent attacks of pain in the left side of the chest under the breast with radiation to the left shoulder produced by physical exertion or mental strain She also had shortness of breath on exertion or mental strain The diagnosis of angina pectoris on the basis of arterio sclerotic heart disease was made elsewhere Three months previously she first experienced an attack of intense pain in the right upper abdominal quadrant accompanied by nausea and slight jaundice She had more such episodes, and the diagnosis of cholelithiasis was made A cholecystectomy and choledochostomy were performed stones were found in the gallbladder but not in the common duct Following operation the patient had no further attacks of pain in the precordium A pressure study of the common duct was made and when the pressure was raised to a level of 400 mm of water pressure the preoperative anginal type of pain recurred and ceased immediately on reduction of pressure The ballistocardiographic tracing showed no abnormality before operation, after operation or simultaneously with the rise in pressure and the electrocardiograph was negative Subsequently the patient was found to be completely relieved of pain

The authors believe that these are the first reported cases in which anginal attacks have been consistently reproduced experimentally in a man by distention of the common duct It can now safely be concluded that gallstone disease or diseases of the common duct may aggravate the symptoms of preexisting heart disease Reflexes arising in the extrahepatic bile passages may at times bring about a restriction in coronary blood flow which produces the symptoms of angina pectoris When

(8) Ann Surg 115 10 1065 J 194

the extrinsic factors giving rise to these reflexes are removed the anginal symptoms disappear Similarly such reflexes may further decrease the coronary blood flow brought about by intrinsic changes in the coronary vessels While adequate surgery does not completely relieve the patient of his cardiac symptoms some measure of relief is nearly invariably obtained

Determination of Urobilinogen in Feces and Urine Comparison of the Sparkman and the Watson Procedure C J Watson and Eleanor Pilden[9] (Univ of Minnesota) made direct comparison of the Sparkman and the Watson procedure for estimation of urobilinogen in feces and urine Sparkman advocated single determinations of urobilinogen in individual specimens of feces expressing the content in milligrams per 100 Gm The amount in 24 hour specimens of urine is expressed in milligrams per 100 cc Sparkman s method does not provide for concentration of small amounts of urobilinogen from either feces or urine The authors had insuperable difficulty in making the color comparisons with this method The standard which contains gold chloride presumably to compensate for disturbing yellow colors from the urine or feces was too yellow Comparisons of samples with lesser concentrations of urobilinogen were found to be impossible A rough estimation was possible with higher concentrations The authors carried out determinations on acholic feces containing significant small amounts of urobilinogen giving only qualitative descriptions since color comparisons were impossible with the Sparkman standard

The results indicate that the Sparkman procedure is not sufficiently sensitive in detection of small but significant amounts of urobilinogen in either feces or urine In one case the reaction was negative although the sample was found to contain 7 1 mg by the Watson technic The authors were unable to confirm Spark

(9) A h I t M d 68 740 46 Oct be 1941

man's conclusion that his technic yields higher values for urobilinogen in both feces and urine than does the Watson procedure In fact their results showed the opposite The high values reported by Sparkman may possibly depend on an error in colorimetric determination related to the yellow color of the standard solution Variable concentration of the urine and hence of its yellow pigment contributed further to poor color comparison These factors probably account for the values reported for normal urine, which are undoubtedly much too high i e, 5 20 mg per 24 hours In the authors' experience the color comparison in the case of normal urine has not been possible with the Sparkman method They believe that a simple qualitative test used serially or at frequent intervals would be most helpful In using the qualitative test however the possibility must be remembered that dilution may give rise to a negative result in the presence of a significant increase and, conversely that concentration may unduly emphasize an insignificant amount

Comparative Evaluation of the New Liver Function Tests John G Mateer James I Baltz Donald F Marion, Robert A Hollands and Elizabeth M Yagle[1] (Henry Ford Hosp) present a comparison of the intravenous hippuric acid test the cephalin cholesterol flocculation test the colloidal gold test and a serial bromsulfalein test with the oral hippuric acid test and the Rosenthal bromsulfalein test Their results indicate that the cephalin cholesterol flocculation test the intravenous hippuric acid test and the serial bromsulfalein test are best for routine determination of hepatic function These three newer tests are much more sensitive than the two older ones i e the Rosenthal bromsulfalein and the oral hippuric acid test The newer tests are reliable

In any comprehensive evaluation of suspected liver damage in nonjaundiced patients all three of the newer

(1) Am J D g st D 9 13 29 J nuary 194

tests should be used For jaundiced patients the cephalin flocculation test and the intravenous hippuric acid test should be used The bromsulfalein test is not reliable in the presence of jaundice The colloidal gold test is not well adapted for routine clinical use Too much time and effort are required for the necessarily frequent restandardization of the gold solution every two weeks and for the simultaneous conduct of 10 to 20 normal control tests each time these repeated normal control studies are necessary to insure reliable results The oral hippuric acid test should be used in selected cases in which a less sensitive test is advantageous particularly in cases with appreciable known liver damage the operative prognosis of which needs to be determined The Rosenthal bromsulfalein test is reliable when it is positive but because of lack of sensitivity and of any advantage over the much more sensitive and at the same time reliable serial bromsulfalein test it should be replaced by the serial method

[There is no doubt that these modifications of familiar tests are improvements over the original tests In a postscript the authors stron ly recommend the use of unripened cephalin in the conduct of the cephalin cholesterol flocculation test because ripened cephalin preparations yielded several times as many false pos t ve re actions as the unripened preparation in their experience In a recent letter Mateer emphasized on the bas s of control studies that the ripened cephalin is enti ely too sens t ve and therefore quite unrel able Apparently further critical investigations of a similar nature will have to be arried out before the value of this test as a routine diagnostic procedure can be properly app aised —Ed]

High Fat Diet Preceding Cholecystography Howard Curl (Univ of Tennessee) reviews the literature and experimental studies made on filling the normal gall bladder He concludes that fat is an essential factor in the gallbladder emptying mechanism Patients on a fat free or low fat diet may have a gallbladder which not emptied for days may be distended with thick concentrated bile such a gallbladder unable to admit

(2) J A M A 119 607 610 Ju e 20 1942

more bile will not be visualized on the film Before examination all patients should be put on a high fat diet for several days or even weeks

[Published reports indicate that about 10 per cent of nonvisualized gallbladders have later proved to be free from pathologic changes When the clinical evidence for cholecystic disease is not convincing cholecystographic examination could reasonably be repeated after carrying out the measure advocated by Curl Six years ago Jenkinson pointed out the usefulness of a diet rich in fat if tolerated Conversely a normal cholecystographic response is occasionally obtained in the presence of a pathologic gall bladder surgically verified under circumstances previously pointed out by this reviewer —Ed]

Choledocholithiasis J Edward Berk[3] (Jefferson Med College) states that common duct stones may be present in a considerable number of patients in whom there is no clinical suspicion of their existence A certain proportion of the unfavorable results following surgery of the gallbladder for both acute and chronic disease may be attributed to common duct stones overlooked at the primary operation More thorough examination of the common duct is required Berk considers the incidence and symptoms of common duct stone to establish and justify several indications for exploring the common duct at the time of primary operation on the gallbladder

The operative experience of a group of representative surgeons reporting from various large clinics is summarized It shows that common duct stones are found in about 1 of every 10 patients with acute cholecystitis In only 30 per cent the duct was explored, yet in one third of these calculi were recovered Positive recovery of stones may possibly increase as more ducts are explored The frequency with which ductal calculi occur in patients with acute cholecystitis offers a serious objection to the routine application of early or emergency operation advocated by some surgeons In some patients the edema and swelling in the early acute phase prevent anything more than a cholecystos

(3) Am. J S rg 55 96 101 Ja uary 194

tomy and it is impossible to make an adequate and satisfactory exploration of the common duct

The reported findings of several surgeons working in large hospitals show that only a little over 30 per cent of the ducts were explored at the time of operation on the gallbladder for chronic cholecystitis yet calculi were recovered from almost 40 per cent of those explored *Practically one in eight of all patients* with chronic cholecystitis may be expected to have one or more stones in the common duct Many negative explorations will have to be made to accomplish a high percentage of complete removal of ductal stones and a low percentage of return of symptoms after cholecystectomy

The classic triad of signs and symptom ascribed to common duct stones consists of jaundice colic chills and fever Analysis of the frequency of these symptoms is made Concerning jaundice it is noteworthy that about one of every four patients with choledocholithiasis will at no time display any jaundice Zollinger has recently offered a compilation of justifiable indi*cations for exploration of the common duct According* to this the clinical history must include (1) history or presence of jaundice (2) cholangitis associated with cholelithiasis (3) recurrent symptoms after cholecystectomy (4) frequent attacks of gallstone colic (5) pronounced involuntary vomiting With such a history the findings at operation will include (1) suspicion of stone by *palpation (2) dilated or thickened com*mon duct (3) contracted thickened gallbladder (4) dilated cystic duct (5) loss of normal appearance of aspirated bile (6) thickening of the head of the pancreas (7) many small stones in gallbladder and the cystic duct

The addition of choledochostomy to the primary gallbladder operation does not add to the risk in the hands of competent surgeons No one should undertake to operate on the gallbladder who is not capable at the

same time of successfully performing operative procedures on the biliary ducts whenever necessary

Left Sided Pain in Biliary Tract Disease Although the pain in biliary tract disease is primarily epigastric or right sided, occasionally there is a left sided component in the pattern of pain reference When this happens either pancreatitis or an extension of the pericholecystic inflammation to the left side is generally a sufficient cause However pain only on the left side may occur without an inflammatory process In such rare cases the origin of the pain in the biliary tract may be overlooked because of the clinical habit of regarding the latter as possessing an exclusive right sided innervation On embryologic grounds, the common duct must be assumed to have a bilateral innervation This provides a reasonable explanation for some cases of bilateral pain in noninflammatory disturbances of the biliary ducts and for the occasional case in which there is an exclusively left sided reference

Jacob Fine and Arnold Starr[4] (Beth Israel Hosp Boston) report two cases of stone in the common duct In one pain was referred only to the left side and in the other to both sides with equal intensity In the latter distention of the common duct postoperatively produced pain on the left side only

[The fact that pain may be limited to the left upper quadrant in calculous cholecystitis has previously been commented on Such an unusual though infrequent location of pain also occurs in lesions of other organs such as the kidney stomach and duodenum Under such circumstances of course diagnostic difficulties are enhanced Tenderness of a contralateral nature is also a generally recognized phenomenon —Ed]

Biliary Dyskinesia According to F J Holroyd (Princeton) the diagnosis of biliary dyskinesia can usually be made by the characteristic location of pain in the right subcostal region extending around into the right scapular region Sometimes the pain may be localized in the region of the right kidney Differentia

(4) New E gland J Med 25 330 33 A g 8 194'
(5) We t V g n a M J 37 407 409 Sept mber 194

tion from colic due to stones or chronic infection may be difficult and is made by roentgen studies which include the Graham Cole test and studies of duodenal drainage The most characteristic symptom of functional biliary dyskinesia is headache Many patients have had the gallbladder drained or removed without relief from symptoms A characteristic attack of colic can usually be induced in 5 to 30 minutes by hypodermic injection of 0 01 Gm morphine sulfate which causes a spasm of the sphincter of Oddi and the mid portion of the duodenum Larger doses of morphine will decrease the sensibility to pain but prolong and augment the increase in pressure in the common bile duct A spontaneous or induced spasm is usually relieved by inhalation of amyl nitrite or by sublingual administration of 0 0005 Gm glyceryl trinitrate Since biliary dyskinesia is usually associated with and influenced by chronic atonic or spastic constipation normal gastro intestinal habits should be developed The diet should be adjusted according to the patient s weight The asthenic underweight person should have plenty of uncooked fats to build up his weight and stimulate his probably atonic gallbladder Weight loss in obese patients often helps the gallbladder to function Administration of barbiturates and atropine before meals may be useful for mild sedation and symptomatic relief Taking olive oil before meals or magnesium sulfate before breakfast may lessen the severity of the attacks Bile salts may be of value in stimulating the liver and possibly relaxing the sphincter of the bile duct The best drug for prevention of attacks is 0 00027 Gm glyceryl trinitrate taken sublingually every three hours for three days and then after meals and at bedtime for three weeks This course of treatment often produces permanent relief in many cases provided there is no stone in the common bile duct The treatment may also be temporarily useful in cholelithiasis when surgical intervention is inadvisable because of hyperten

sion thrombosis of the coronary vessels disease of the kidneys or the advanced age of the patient

Cruveilhier Baumgarten Syndrome Review of Literature and Report of Two Additional Cases Eugene L Armstrong W L Adams Jr L J Tragerman and E W Townsend[6] (Univ of Southern California) believe that the term *Cruveilhier Baumgarten syndrome* may be applied to patients having a clinical picture of *portal hypertension featured by a loud abdominal murmur* and thrill The second case reported by the authors fulfils these criteria and *becomes the fifth case* of Cruveilhier Baumgarten *disease* on record both cases increase the total number of reported cases of the *syndrome* to 55 Preservation of the name as applied to the syndrome is indicated because of the fairly uniform clinical picture centered about the loud murmur and thrill More important is the advisability of maintaining the integrity of a distinct disease of separate etiology and pathologic features as delineated in the picture of Cruveilhier Baumgarten *disease*

A resume of all cases including the present two, *shows the age of the patients to vary from 15 to 70* years the greatest number being between 40 and 49 The following symptoms were described most frequently abdominal swelling 13 cases epigastric pain and/or digestive disturbance 12 hematemesis 10 jaundice 10 weakness 8 prominent abdominal veins 6 loss of weight 4 No symptoms were recorded in 27 cases Of the physical findings abdominal venous murmurs were described in 44 cases with the following distribution of *location* epigastric 26 umbilical 14 epigastric and umbilical 9 and elsewhere in the abdomen 8 Palpably *enlarged spleen* was *described* in 31 cases palpable thrill in 24 distended superficial thoraco abdominal veins in 23 palpable liver in 20 ascites in 15 peripheral edema in 7 and caput medusae in 3 Secondary anemia was present in 13 cases and leukopenia

(6) Ann Int Med 16 113 151 Ja ry 1942

in 10 and a positive Wassermann reaction was obtained in 9 The antemortem diagnoses in the 55 cases were cirrhosis 18 cases Cruveilhier Baumgarten disease 13 Banti s disease 4 undetermined 18 nephritis 1 congenital syphilis 1 In 32 cases in which autopsy was performed the causes of death were gastric hemor



Fig 159 —I f ed ph t gr ph w h f l d t m m

rhage 5 hepatic insufficiency 2 pneumonia 1 pneumococcic sepsis 1 pulmonary edema 1 peritonitis 1 bronchitis 1 postoperative 1 and not stated 19

Analysis of the pathologic data shows that the liver was normal in size in 2 cases small in 20 and enlarged in 1 In 15 cases the surface was nodular and in 3 smooth In 15 cases the liver was described as grossly cirrhotic General atrophy was noted in three cases atrophy of

sion thrombosis of the coronary vessels disease of the kidneys or the advanced age of the patient

Cruveilhier Baumgarten Syndrome Review of Literature and Report of Two Additional Cases Eugene L Armstrong W L Adams Jr, L J Trageman and E W Townsend[6] (Univ of Southern California) believe that the term Cruveilhier Baumgarten syndrome may be applied to patients having a clinical picture of portal hypertension featured by a loud abdominal murmur and thrill The second case reported by the authors fulfils these criteria and becomes the fifth case of Cruveilhier Baumgarten *disease* on record both cases increase the total number of reported cases of the *syndrome* to 55 Preservation of the name as applied to the syndrome is indicated because of the fairly uniform clinical picture centered about the loud murmur and thrill More important is the advisability of maintaining the integrity of a distinct disease of separate etiology and pathologic features as delineated in the picture of Cruveilhier Baumgarten *disease*

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(6) Ann I t Med 16 113 1 1 J nua y 1942

right branch twice and thrombosis or stenosis of the hepatic veins three times The umbilical vein itself was recorded as patent in 14 cases partially patent in 2 and obliterated in 1 A large patent para umbilical vein was described in nine cases The spleen was grossly enlarged in 18 cases normal in 1 and small in none it showed chronic passive hyperemia in 1 and was not described in 9 cases *Microscopically* the spleen was normal in one case and was cellular with increase of pulp in one it showed fibro adenia in one case thickening of trabeculae in one fibrosis in four chronic passive hyperemia in one and shrunken pulp in one

Treatment consists largely of attempts to alleviate symptomatically the dominant picture that of progressive and usually fatal portal decompensation Splenectomy is thought valueless and particularly contraindicated because of danger of hemorrhage from the greatly dilated venous channels in the abdominal wall Caution must be observed to avoid the large veins when doing paracentesis or peritoneoscopy Peritoneoscopy may be of value in demonstrating a large umbilical vein and in permitting biopsy of the liver in suspected cases of Cruveilhier Baumgarten syndrome

Clinical Detection of Hepatic Disease in Hepatolenticular Degeneration. William H Sweet Seymour J Gray and J Garrott Allen[7] (Univ of Chicago) state that despite the prominent role attributed to the liver in hepatolenticular degeneration symptomatic evidence of hepatic disease is slight or entirely absent Only occasionally is there a history of jaundice prior to onset of neurologic symptoms The authors report nine cases which indicate that definite evidence of cirrhosis of the liver can be demonstrated conclusively by the newer tests of hepatic function particularly Gray s serum colloidal gold test and the serial dilution one stage technic for prothrombin time Four cases had been mistakenly diagnosed as chronic encephalitis

(7) J A M A 117 1613 1619 Nov 8 1941

the left lobe alone in four and of the right lobe alone in four Hypertrophy of the left lobe was mentioned in one case and chronic passive hyperemia in one Microscopically cirrhosis was noted four times, "fibro

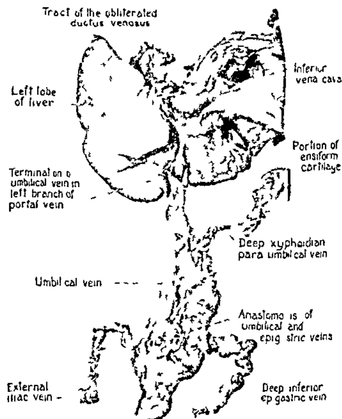


Fig 160 — Co ect o s of p t nt umbili l ve n w th thora o-abdominal e d po t l ve

sis' three times and atrophy three times The portal vein was recorded as grossly normal in 6 cases and ab normal in 2 it was not described in 21 Thrombosis of the portal vein was described twice hypoplasia of the

lions presumably the same structures affected in hepatolenticular degeneration In only one of the control cases was there an abnormal result and repetition of the test did not confirm the first positive reaction The test gave *positive results on two or more occasions in eight of the* nine case of hepatolenticular degeneration In the one case in which the reaction was negative hepatic dis ease was demonstrated by other methods A positive reaction is represented by the flocculation of colloidal *gold when serial dilutions of blood serum are added to it giving a curve (543 or 532) similar to the dementia* paralytica curve obtained with spinal fluid Normally little or no flocculation occurs Plasma protein levels and the cholesterol cholesterol ester partition proved to be of little or no value in detecting hepatic disease in hepato lenticular degeneration The galactose tolerance brom sulfalein retention or hippuric acid tests proved to be far less sensitive than the serum colloidal gold pro thrombin time and bilirubin excretion tests

Development of Cirrhosis of the Liver after Acute Hepatitis Determined by Aspiration Biopsy N B Krarup *and* K Roholm[8] *examined* 12 patients with grave protracted or recurring hepatitis They found a gradual transition from the usual acute hepatitis to fully developed Laennec s cirrhosis Decided chronic changes may develop in the course of weeks but the de *velopment of cirrhosis may also extend insidiously over* several years The possibility of chronic hepatitis must be kept in mind when the course of hepatitis is prolonged or when the condition shows a tendency to recur rence None of the patients in this series was addicted *to the use of alcohol*

[Cirrhos s of the liver (chronic hepat t s) is usually the terminal stage of a long stand ng process the ea ly course of which is *symptomless Onset is ob cure is mo t cases Alcohol cinchophen* syphilis other familiar hepatotoxin and infect ons play no demonstrable role A history of antecedent catarrhal jaundice (acute hepatitis) or jaundice from any cause is sign ficant

(8) N d m d (H j t l t d) 10 1991 00 J 8 1941

It might be contended that with any patient presenting only neurologic symptoms there is no way of knowing that hepatic disease is already present Results of the study of these nine cases favor the conclusion now generally held that hepatic cirrhosis always occurs first and that the lenticular lesions follow In numerous cases cirrhosis of the liver has been demonstrated either at operation or on physical examination and only subsequently have neurologic symptoms developed In several families in which one or more members presented the fully developed picture of hepatolenticular degeneration others had died early in life from hepatic cirrhosis before neurologic symptoms appeared In other cases there was definite history of jaundice prior to onset of any neurologic symptoms Some of the cases showed a further characteristic feature the so called Kayser Fleischer ring a deposition of yellowish brown or greenish brown pigment in Descemet s membrane near the limbus of one or both corneas, which in the presence of signs of extrapyramidal disease is pathognomonic of hepatolenticular degeneration This ring was seen in four of the nine cases

The serum colloidal gold test of Gray has given positive results in a higher percentage of cases of clinical cirrhosis of the liver than any other test heretofore reported Many of these cases of hepatic cirrhosis have been confirmed by autopsy or biopsy The ease of performance of the test makes the accumulation of an enormous series of control observations possible over 300 on normal persons and patients with diseases unassociated with pathologic conditions of the liver The presence of a normal liver was demonstrated in a large number of these cases at autopsy or biopsy This series of controls included patients with numerous miscellaneous neurologic disorders among whom were six with paralysis agitans and four with parkinsonism following a definite attack of acute epidemic encephalitis In these disorders the lesions involved the basal gang

Results in 50 patients, seen during the latter part of 1938 and during 1939 and 1940 have been studied In January 1941, 30 of the patients were dead and 20 living Fifty five per cent of the 20 living patients were improved markedly the remaining 45 per cent gave little evidence that the course of the disease had been altered Average duration of life in cases in which death occurred was disappointingly small probably be cause of the advanced stage of the hepatic lesion at first examination About three times as many patients con *sidered on a percentage basis* were *free from ascites* and enjoying a reasonably normal existence as in any other group of cases of cirrhosis in which results of treatment have been reviewed at the Clinic

The continuance of a primary dietetic program of this type is not easy The patients often require pro longed hospital care careful nursing and meticulous at tention to the details of treatment Improvement is slow and patience optimism and persistence are obviously necessary for both patient and physician Earlier diag nosis is imperative if therapeutic results are to be im proved obviously much more attention should be paid to patients with mild digestive disturbances slight loss of weight and a palpable liver or spleen

Treatment of Cirrhosis of the Liver by a Nutritious Diet and Supplements Rich in Vitamin B Complex Arthur J Patek Jr and Joseph Post[1] (Columbia Univ) state that this treatment is of value as shown by a comparison of 54 patients so treated with 386 controls with the same disease Following onset of ascites 72 per cent of the treated series as compared with 57 per cent of the controls survived six months At the end of the first year 57 per cent of the treated series survived but only 39 per cent of the controls At the end of the second year 45 per cent of the treated series as compared with 21 per cent of the controls were still alive

Aside from the increased period of survival there were

(1) J Clin In stig t n 0 481 505 Septemb 1941

Kornberg (1942) states that persons long recovered from catarrhal jaundice show an abnormal retention of bilirubin and possess symptoms of liver dysfunction in a considerable percentage of the cases Bloomfield's instructive contribution (1938) on the natural history of chronic hepatitis furnishes profitable reading in connection with the foregoing —Ed]

Recent Trends in Treatment of Cirrhosis of the Liver

Treatment has changed considerably during the past three years according to H R Butt and A M Snell[9] Treatment devoted principally to elimination of ascites by mercurial diuretics, restriction of fluids and purgation has been largely abandoned, and reliance has been placed chiefly on a diet high in carbohydrate and protein together with administration of large doses of vitamin supplements The general plan of treatment follows

TREATMENT —The patient has been provided with a diet containing 350 500 Gm carbohydrate, 110 145 Gm protein, chiefly of vegetable origin or derived from milk or egg white and about 60 mg fat About 50 per cent of the protein is now derived from meat, because of difficulties in preparation Rather large doses of vitamin supplements are added Vitamins A and D as concentrated fish liver oil have been given in doses of 25 000 to 50 000 I U once or twice a day Thiamine hydrochloride is given by mouth in doses of 1 mg 10 times daily Citrus fruit juices in doses of 8 to 12 fl oz daily supply the ascorbic acid Brewers' yeast, either in tablet form or in the powdered form mixed with tomato juice or eggnogs prepared with milk has been given in doses of 30 to 50 Gm. a day Liquid concentrates of yeast have been used in varying doses A few patients have received niacin amide Practically all patients have been given liver extract either as an aqueous solution by mouth in a dose of 1 fl oz three times daily, or by parenteral injection of the crude aqueous extract of liver (campolon) This has been given intramuscularly in doses ranging from 3 to 5 cc two or three times a week While patients are hospitalized this material together with solutions of glucose, is administered intravenously

Acutely ill patients receive solutions of glucose intravenously while hospitalized in many cases suitable amounts of niacin amide and thiamine hydrochloride are given in the solution of glucose

(9) Proc. Staff Meet Mayo Clin 17 2 0 254 Apr 1942

TABLE 1—STANDARD SEMILIQUID DIET FOR PATIENTS WITH CIRRHOSIS

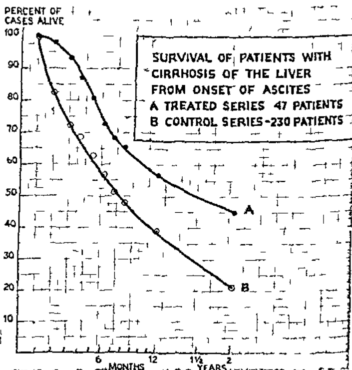
			P o-EINS	F s	C BO-Y
7 a m	M lk	200 c	6 0	8 0	10 0
8 m	Cer al (pabl m)	100 Gm	2 0	1 0	11 0
	S gar	1 Gm			1? 0
	Cream 20%	30 cc	1 0	6 0	1 0
	Egg	2	13 0	10 0	
9 a m	Orange ju ce	00 cc			18 0
10 a m	Egg og				
	M lk	150 cc	4 5	6 0	5
	Egg	1	6 5	6 0	
	Sug	10 Gm			10 0
	Brewers yeast	Gm	1 5	0 5	8 5
11 a m	Cream soup	00 cc	6 0	14 0	15 0
	Ma h d p tatoes	100 Gm	? 0	6 0	15 0
	Butter	10 Gm		8 5	
	Puréed v getable	100 Gm			4 0
	Or ge ju c	00 c			18 0
12 noon	Cocomalt	00 cc	6 0	10 0	0 0
2 p m	Egg og	00	11 0	11 0	17 5
3 p m	O nge ju c	200 cc			18 0
4 p m	C l (p bl m)	100 Gm	2 0	1 0	11 0
	S g r	12 Gm			12 0
	Cream 0%	30 c	1 0	6 0	1 0
	Jello	100 Gm	1 0		18 0
	C m ?0%	30 c	1 0	6 0	1 0
	O nge juice	00 cc			18 0
5 p m	Cocomalt	00	6 0	10 0	0 0
6 p m	Eggnog	?00	11 0	11 0	17 5
	Brew y t	5 Gm	1	0 5	8 5
7 p m	Egg g	00 c	11 0	11 0	17 5
	G d total		116	131	315

C l es 903

Th sem l q d d t w d ly th pt l wh p t t th f d w ble t t k th l d d t B w rs y t w f d milk g Th y ast was tir d th ghly ld milk d fl d w th g illa d tm g

the liver was striking but the relation of this nutritional deficiency to the cirrhosis is not clear Apparently nutri tional deficiency predisposes to the development of cir rhosis and cirrhosis once established tends to perpetu ate the state of nutrition il deficiency The etiologic

signs of general bodily improvement and presumptive evidence of arrest of the disease In a significant number of patients ascites edema, jaundice and 'vascular spiders' disappeared The level of the serum albumin and serum globulin the Takata Ara test cephalin floc



F g 161 —S i l fte nset f sc t s n p tie ts w th c rrh s f l r C mputat ons bey d ond y r not u ed b ue numb in t at d ser e was too small

culation test and bromsulfalein dye test reflected corresponding improvement Thus it appears that hepatic cirrhosis is not necessarily committed to a continuous, progressive course

Coexistence of nutritional deficiency and cirrhosis of

relation, if it exists between nutritional deficiency and cirrhosis could be either direct or indirect Possibly lack of certain food factors leads directly to development of *cirrhosis It is also possible that the malnourished* liver becomes vulnerable to toxins which ordinarily would be destroyed

The tables outline the dietary regimen used The diet differs radically from that commonly advocated in the United States for treatment of cirrhosis of the liver which is high in carbohydrate but low in protein and fat The present diet contains a moderate amount of protein and fat In addition to the protein the patients received 50 Gm powdered brewers yeast daily of which the protein content is about 50 per cent There was no *evidence of intolerance to fat in the amounts given* Salt intake was restricted in patients with ascites and edema to the extent of omitting a salt shaker from the tray and fluids were allowed up to 2 000 cc daily In addition to the yeast the patients generally received intramuscular injections of concentrated liver extract 5 cc twice weekly and of thiamine hydrochloride 5 mg daily In patients with severe neuritis thiamine hydrochloride was given in doses of 10 to 20 mg daily

Surgical Aspects of Acute Pancreatitis are discussed by Robert Elman (Washington Univ) with special *reference to its frequency* as *revealed by the serum* amylase test Physicians are urged always to consider the pancreas as a cause of severe pain in the upper part of the abdomen The frequency of acute pancreatitis is not generally realized because this disease so mimics other acute conditions that a clinical diagnosis can seldom be made without the serum amylase test which reveals a high value soon after onset of the attack The clinical manifestations of acute pancreatitis are usually those of an acute surgical condition within the abdomen such as perforated peptic ulcer acute intestinal obstruction

(2) J A M A 118 1265 1 68 Ap 11 1942

TABLE 2—STANDARD SOLID DIET FOR PATIENTS WITH CIRRHO IS

		PROTEINS	FATS	C RBOHYDRATES
Breakfast				
Fruit 18%	1 serving			18 0
Cooked cereal or	200 Gm.	4 0	2 0	20 0
Prepared cereal	30 Gm			
Sugar on cereal	12 Gm.			1- 0
Eggs	2 only	13 0	10 0	
Milk	-00 cc	6 0	8 0	10 0
Toast	60 Gm	4 0	1 0	30 0
Butter	°0 Gm		17 0	
Coffee				
Cream 20%	u0 cc	1 0	6 0	1 0
Sugar	12 Gm			1 0
9 a m Brewers yeast	25 Gm	12 5	0 5	8 5
Milk	1u0 cc	4 5	6 0	7 5
Sugar	12 Gm			1? 0
Dinner				
Meat medium fat	100 Gm.	17 0	-0 0	
Vegetables 5%	100 Gm	1 0		4 0
Vegetables 10%	100 Gm	2 0		9 0
Vegetables 20%	100 Gm	3 0		19 0
Bread	30 Gm	2 0		15 0
Butter	-0 Gm		17 0	
Dessert (cake pudding)	1 serving	5 0	8 0	2o 0
Milk	°00 cc	6 0	8 0	10 0
Coffee				
Cream 20%	u0 cc	1 0	6 0	1 0
Sugar	12 Gm			12 0
2 p m Brewers yeast	-5 Gm	12 5	0 5	8 5
Milk	1u0 cc	4 5	6 0	7 5
Sugar	12 Gm			12 0
3 p m Orange juice	-00 cc.			18 0
Supper				
Soup (julienne)	200 cc	4 0		4 0
Meat medium fat	100 Gm	17 0	-0 0	
Vegetables 5% salad	100 Gm	1 0		4 0
Vegetables 20%	100 Gm	3 0		19 0
Bread	30 Gm	2 0		15 0
Butter	-0 Gm		17 0	
Milk	200 cc	6 0	8 0	10 0
Fruit 18%	100 Gm			18 0
Tea				
Cream 20%	30 cc	1 0	6 0	1 0
Sugar	12 Gm			12 0
7 p m Milk	200 cc	6 0	8 0	10 0
Grand total		139	1"5	365

Calo es 3 591

ulcer and perforation of a gastric or duodenal ulcer or of the gallbladder or ileus seems possible If laparotomy discloses acute pancreatic necrosis the abdominal cavity is closed without further intervention Surgical intervention becomes necessary when a pancreatic abscess develops at a later stage Operation in the interval is likewise indicated if biliary symptoms have not entirely disappeared and if the history suggests disease of the biliary tract. Surgical treatment of biliary tract disease *mitigates the danger of relapse of acute pancreatic* necrosis Medical and dietetic treatment is important *during the early stage Shock is treated by drip infusion* of dextrose and insulin and by circulatory stimulants Atropine may be helpful because it decreases pancreatic secretion and counteracts irritation of the vagus and vascular spasms

Present-Day Surgery of the Pancreas Allen O Whipple[4] (Columbia Univ) discusses the general aspects of the pancreas and states that clinical tests of the external secreting function of the pancreas although still in the experimental stage are contributing materially to the diagnosis of acute and chronic lesions of the organ *Tests for the acute lesions consist of lipase and amylase* determinations in the blood serum while those for the chronic inflammatory lesions and the chronic obstructive lesions of the pancreas use secretin which increases the volume and alkalinity of pancreatic juice and mecholyl which increases the concentration of the ferment without increasing the volume and alkalinity The latter is a more accurate index of the activity of the acinar tissue than of the obstruction of the flow of the pancreatic juice

Acute pancreatitis may vary from acute edema to complete necrosis of the entire organ Shock is the most serious phase of the symptoms and signs and must be treated first Treatment consists of plasma transfusion physiologic saline solution and adrenocortical extract

(4) N w E gl d J M d 6 515 5 6 M 26 194

acute cholecystitis and acute appendicitis, so that often emergency operations are needlessly performed In other instances acute pancreatitis masquerades as a coronary attack or biliary colic and is the cause of the "post cholecystectomy" syndrome Treatment is conservative at the outset of the attack if the manifestations subside promptly as they usually do subsequent study may reveal the need for operation usually cholecystectomy, if the manifestations do not subside necrosis of the pancreas (a rare event) is suspected and operation planned for drainage of the lesser peritoneal cavity The treatment and prevention of the individual attacks of acute nonhemorrhagic pancreatitis thus far are purely medical The patient should be placed on a regimen which has as its purpose maintenance of a more or less constant flow of bile and avoidance of any storage of bile for long periods in the gallbladder Small frequent feedings rather than large meals are recommended For the acute attack glyceryl trinitrate 1/1 000 gr, placed under the tongue and repeated in a few minutes shortly after onset of the attack will often result in dramatic abortion of the attack If the attack has been under way for a number of hours the drug is valueless The patient should carry a number of these tablets with him to be taken as soon as the attack begins

Treatment of Acute Pancreatic Necrosis R Demel[3] states that diagnosis of acute pancreatic necrosis was formerly regarded as an indication for immediate operation Evaluation of results of early operation disclosed a mortality of 52 to 78 per cent and autopsies revealed that the necrotic process was not arrested by operation These observations induced many surgeons to adopt a conservative attitude The tendency now is to put the digestive tract at rest This effects a cure in most cases Even in serious cases operation is postponed until the dangerous acute symptoms have subsided Immediate laparotomy is done only if the diagnosis is not entirely

(3) Med Kl 37 404 406 Ap 18 1941

remembered that more than one tumor may be present. Partial pancreatectomy is not sufficient but the tumor must be excised completely

For malignant tumors of the ampullary region and pancreas the radical operation based on the principle of a wide en bloc removal of the tumors as required in modern cancer surgery is still in an evolutionary stage Many more cases, with five year survivals will be required before valid claims can be made for the operations These patients untreated have an average of six months survival from onset of symptoms until death Many of them are tortured with the uncontrollable itching of obstructive jaundice The considerable risk of 30 to 35 per cent mortality is justified if they can be made comfortable even for a year or two If these patients would be referred to the surgeon before they are studied to death while the cancer is small and localized and before serious illness with weeks of obstructive jaundice develops a far lower operative mortality and a much longer survival would result

One Stage Operation for Cure of Carcinoma of Ampulla of Vater and of Head of Pancreas I Ridgeway Trimble John W Parsons and Claude P Sherman[5] (Baltimore) describe this operation and its use in a patient in whom deprivation of the pancreatic secretion by permanent ligation of the pancreatic duct had for the past 11 months no apparent effect on the digestion of fat carbohydrate and protein

OPERATION — After proper preoperative care and anesthesia a high right rectus incision was made through which an enlarged tense smooth walled gallbladder was found that could not be emptied by pressure The cystic duct was small The common bile duct was greatly dilated seropurulent fluid was aspirated from the duct and gram positive diplococci were found on smear A soft round tumor could be felt within the second portion of the duodenum Through a small longitudinal incision in the duodenum the mass appeared as a papillary growth 3 cm in diameter surrounding the ampulla of Vater frozen sections proved to be adenocarcinoma

(5) S g Gynec. & Ob t 73 711 722 N embe 1941

Serum amylase and lipase readings are of great help in differentiating this condition from other acute upper abdominal lesions Three position films of the abdomen to determine fluid levels in the small intestine in ileus and in subphrenic and subhepatic areas in perforation of the gastro intestinal tract are of help If serum amylase readings are definitely elevated and fluid levels and free air are ruled out by x ray examination, diag nosis of acute pancreatitis can be made the patient can be treated for shock and surgical treatment can be de layed Improvement is often so noticeable that operation can be postponed for associated biliary lesions or for localizing pancreatic inflammation or abscess formation This procedure undoubtedly lowers the otherwise high mortality rate considerably

Operation for pancreatic cysts is difficult and only a small percentage of them can be completely removed because of their deep position their relation to vital structures and their frequent association with large, friable vascular channels When exploring the abdomen, careful inspection of such a cyst must determine whether it is removable If it is cystadenomatous multilocular and involves the major portion of the pancreas removal will result in distressing pancreatic fistula Cystaden omatous cysts in the tail of the pancreas can be removed successfully but not those in the head and body For unilocular cysts that cannot be excised marsupialization or drainage should be used In cases in which the fistulous tract persists it is possible to transplant the tract into the stomach or jejunum Whipple marsupial ized two large dermoid cysts arising from the region of the body of the pancreas and at a second operation, in the same patient obtained permanent cure by excis ing the remaining fistulous tract

In patients with islet cell tumors in whom serious hepatic pituitary adrenal and thyroid disease has been ruled out surgery is indicated and should not be de layed When exploring for these tumors it must be

cut surface of the pancreas was transfixed with mattress stitches of catgut The distal stump of the duodenum was *turned in with a double continuous row of no 0 chromic* catgut, and this closure was reenforced with a layer of mat tress sutures of fine silk A loop of jejunum about 30 cm from Treitz s ligament was brought anterior to the transverse colon and sutured to the open stump of the stomach after the anterior Polya method The stump of the common duct was implanted into the side of the jejunum about 20 cm distal



Fig 163 (Bogg Th mp o p 760)

to the site of the gastrojejunostomy The line of anastomosis was *reenforced by stitching omentum about the suture line* The di tal opening in o the jejunum was close l with inter rupted silk stitches One cigaret drain was in erted into the lesser peritoneal cavity and one placed down to the anastomo sis between the common duct and the jejunum The deeper layers of the wound were closed with catgut and the skin was closed with silk Blood transfusion wa given during the latter part of the op ration (Fig 162)

Convalescence was uneventful except for one severe hemor rhage of undetermined origin which was corrected by blood transfusion The patient was discharged five week after op eration

The duodenum was mobilized and divided between clamps at the distal end of its second portion The resected duodenum was *reflected to the right and the head of the pancreas* removed with it and in the same block the distal 5 cm of

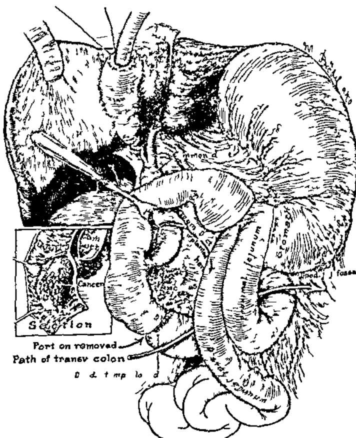


Fig 162.—Resection of d d m pyl c d f t m h c duct and head f p n nt r Poly t mo s Tr lon o tt d f l ty

the stomach The first and second portions of the duodenum and the pyloric portion of the stomach the distal end of the common duct and the head of the pancreas were then resected en masse All bleeding points were ligated with catgut The

DISEASES OF THE INTESTINAL TRACT

Carbon Dioxide Tension and Acid Base Balance of Jejunal Secretions in Man The investigations reported by Lemuel C McGee and A Baird Hastings[7] (Harvard Univ) show that normal human jejunal juice tends to have a characteristic acid base balance with a bicarbonate concentration about one third that of blood serum (8 mm per L) and a carbon dioxide tension about double that of venous blood (100 mm) resulting in a slightly acid pH namely 6 5 These findings are consistent with those previously reported by Robinson and by Herrin for the juice from jejunal loops of dogs Displacement of the normal acid base balance by acid alkaline salts or dilution results in a prompt return of the balance of the juice to normal values It may be inferred therefore that regulation of the composition of the juice is to be regarded as a physiologic phenomenon characteristic of the cells responsible for the formation of the juice The high carbon dioxide tension at which the juice is maintained in the absence of or with the exclusion of gastric juice suggests that the jejunal juice may originate from two sources one of which produces an acid secretion and the other an alkaline secretion The significance of these observations for the maintenance of the normal activity of intestinal enzymes merits further investigation

Occult Blood Use of Carmine for Marking of Stools M Kirschen H Sorter and H Necheles[8] (Michael Reese Hosp Chicago) kept 146 normal persons without gastro-intestinal complaints on meat-free diets until their stools were negative to the routine benzidine slide test Then 1 5 2 Gm hemoglobin (corresponding to 9 4 or 12 5 cc blood with 16 Gm per cent hemoglobin content) was administered orally in five doses evenly dis-

(7) J B l Chem 14 893 904 F bru ry 1942
(8) Am. J D g t D 9 154 156 M y 194

Krukenberg Tumor Originating from a Pancreatic Carcinoma J Boggino and Q Codas Thompson[6] (Paraguay) report an unusual case of Krukenberg tumor in which the primary tumor was located in the pancreas This location is rare

Bilateral ovarian tumors removed from a patient, 37, were identified histologically as typical Krukenberg tumors After three months the patient returned complaining of constipation with diarrheic episodes *nausea and diffuse* abdominal pains Although roentgen examination at this time was negative the symptoms continued and were aggravated Two months later roentgen examination showed a pancreatic tumor (Fig 163) At laparotomy only a small portion of the pancreas was recognizable tissue the neoplasm was the size of an orange lobulated in *appearance* with small fibrogelatinous papillae It had invaded the omentum, although only small plaques were observed on the gastric serosa The pelvic peritoneum was thickened by the neoplasm, which showed *an irregular lobulated surface A biopsy specimen of the* pancreatic tumor was removed Histologically, it showed small nests of mucigenous cells in an abundant fibrous connective tissue stroma with some fat cells interspersed (Fig 164) The patient died a month later



Fig 164—Tumor of pancreas

(6) Bol I t de med per par el stud y trat d cá cer 16 779 789 September 1941

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(7) J B l Chem 14 893 904 F bru ry 1942
(8) Am J Digest D 9 154 1 6 M y 1942

tributed over one day All stools were examined during the following five days Of the group, 41 per cent had occult blood in their feces while 59 per cent had none Thus these rather large amounts of hemoglobin more or less lose their ability to give a positive peroxidase reaction after passing through the gastro intestinal tract. Apparently blood discharged in small amounts from lesions of the gastro intestinal tract will undergo the same changes on its way throughout the stomach and intestines and may therefore not be detected in the feces by the routine benzidine test

Evidently all tests for blood in the stools have a relative value only as none of them can detect amounts of blood below certain limits Furthermore different individuals are able to destroy varying amounts of hemoglobin in their alimentary tract, thus whatever method is used for detection of occult bleedings the clinician must be aware of the relative value of all methods and must not rely entirely on negative stool tests when for example a small bleeding carcinoma of the alimentary tract is suspected but must use his clinical judgment and all other available laboratory methods such as x ray examination gastroscopy etc as well In suspicious cases with a negative peroxidase test more attention must be paid to the clinical or laboratory findings The feeding of 1 5 Gm hemoglobin should be used to determine whether the individual does not destroy unusually large amounts of hemoglobin in his intestinal tract Another test is to administer 10 cc castor oil after three meat free days and to repeat the peroxidase test

Carmine has been used to mark the feces when meat free diet was instituted in some cases A number of preparations of carmine when given by mouth were able to produce positive peroxidase reactions in the stools When these preparations were tested in vitro some yielded positive peroxidase reactions, while others did not, the latter must have undergone a change in the alimentary tract which made them acquire peroxidase

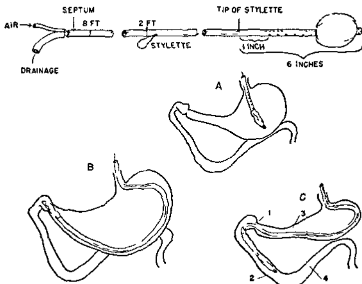
characteristics Recently it has been reported that carmine reduced gastric emptying time and lowered intestinal motility in children These results add to the objections to use of carmine in certain experiments

Indications for Use of Miller Abbott Tube W Osler Abbott[9] (Univ of Pennsylvania) states that intubation of the small intestine was developed as a technic for studying the physiology of the digestive organs from the results have grown diagnostic and therapeutic procedures The diagnostic indications for intubation are aimed at detection of disorders of absorption minimal lesions ill defined by roentgenoscopy advanced intestinal obstructions forbidding the use of opaque meals and rare gastro intestinal disorders unidentifiable by standard methods of study The therapeutic indications aim to forestall expected ileus incident to abdominal disease to safeguard against leakage through intestinal suture lines to abolish paralytic ileus to control distention in mechanical obstructions and to feed patients with peritonitis over long periods while the inflammation is subsiding

Thorough experience with the many difficulties and minor variations of the technic of passing the tube is required Development of a stylet for use in long intestinal tubes (Fig 165) has somewhat decreased the difficulties of insertion With this instrument the tip of the tube can be brought to the duodenojejunal junction usually within 10 to 20 minutes Failure to accomplish this occurred in only 2 of 18 severely ill patients with both obstructing peritonitis and mechanical obstruction In the remaining 16 it was possible to pass the tip promptly to the distal duodenum although previous experience had indicated that it would require many hours to do so Since a stylet in a gastro intestinal tube is a dangerous instrument potentially and since it is often far better for the patient if the stomach is thoroughly decompressed before the tip advances to the

(9) N w E gl d J M d 5 641 646 O t 3 1941

duodenum use of this procedure should not be routine In the desperately ill patient, however, the ability to decompress the small intestine without delay may be crucial in determining the outcome



F g 165 —Techn f us ng tylette n p s ng Mille Abb tt tub P erce wall f a pirat lum n f tube at ft ma k w th l gth of 0 4 mm d mete pec lly tra htened ta nl s teel vom II fe leader w e d advanc t p of w e to po t 1 bo m t p oximal a p rat ng h le in tube b d loop n ther end of wi that t p cann t d nce distally term nal 6 n f M lle Abb tt tube w ll then conta n n w P s tub in usu l m nn r to pos t on n *A* W th tempora y dh si e t p patch o er po nt at wh h st lett p t be wall nject 300 c a r int st m ach and d n t be unt l t l s along gr t cu tu s in *B* Hold tube n p t e t no e t p e t l pp g and pr ly u t on t remo e a r Stom h tr t a n *C* sq e g t p f t b head f m pos *t on 1 to 2 t p f stylett* then l es at *1* A t l p *m w th conc t e e n* tract on d stal t *3* p e ent t m al 6 n fr m o l g a d styl tte p e ent o l ng f tube p ox m l t ntrum whe t mach more flacc d Draw back tip f stylette f m *1* t *3* nd by ge tle t dy pres u o tube at n e advance t p *f om 2* to *4* W thd aw tyl tte, p t h hol through wh *ch t was nt od c d w th th n* rubbe nd *ha ag* *fi tel* balloon w th 0 cc a r I ed a usu l

Serodiagnosis of Trichinosis by Means of Complement Fixation Ernest Witebsky, Philip Wels and Anne Heide[1] (Univ of Buffalo) developed a comple

(1) N w Yo k Stat J Med. 42 431 435 M r 1 1942

ment fixation test Serums from infested human beings as well as from experimentally infested rabbits were examined Trichinella larvae were obtained by infesting rats with trichinous meat the rats were killed five to six weeks later They were skinned and eviscerated and the remainder of the carcass was minced in a meat grinder The ground meat was placed in a funnel over a perforated porcelain plate Digestive fluid was prepared by adding pepsin and hydrochloric acid to tap water and the apparatus containing the material was placed in the incubator at 37 C for one day The larvae were liberated from their cysts by the digestive fluid and fell into a small centrifuge tube they were then washed and dried in a desiccator Watery extracts were prepared from the dried and powdered larvae The clear supernatant fluid obtained from further decanting and precipitation was used as the antigen in the experiments

The antigen was used in seven cases of trichinosis In two the diagnosis was confirmed by biopsy in three no biopsy was performed but clinical manifestations and history were suggestive of trichinosis Two cases were of special interest since negative tests were obtained before antibodies became demonstrable in the patients serum In one case it took six weeks for the test to become positive in a serum dilution of 1 5 The antibody titer of this patient rose 10 weeks after infestation to 1 640 The first positive serum specimen with a titer of 1 5 was examined with decreasing amounts of antigen and a constant amount of serum dilution (1 5) In this order of experiment the patient s serum reacted with an antigen dilution up to 1 8 000

Two different methods were tried to determine how the complement fixation test for trichinosis would work as an abbreviated routine procedure in serodiagnostic practice The first method consisted of mixing several dilutions of boiled trichinella antigen with a constant serum dilution The second consisted of mixing decreas

ing amounts of serum dilution with a constant amount of trichinella antigen. Both methods seem to be feasible and might be recommended In the first a 1 500 and a 1 2 000 dilution of trichinella antigen were mixed with a 1 5 or 1 10 dilution of inactivated patient serum the preparation was kept for about two hours in the refrigerator and then placed in the incubator for one hour In the second method a 1 2 000 dilution of boiled trichinella antigen was mixed with serial dilutions of patient s serum such as 1 5 1 10 and 1 20 The latter method is preferred Of 1 000 human serums examined in this way as controls only 1 gave a definite positive reaction in both complement fixation and pre cipitation tests This serum was obtained from a healthy blood donor who gave no history of trichinosis

Basic Problems of Acute Appendicitis Frederick Fitzherbert Boyce and Harry E Nelson[2] (New Orleans) *state that Bower of Philadelphia has probably done* more than any person living to demonstrate how the mortality of acute appendicitis can be reduced How ever they do not agree with Bower that all attention should be concentrated on rupture and peritonitis Peritonitis is the cause of most deaths in acute appendi citis This situation does not prevail because too little attention is paid to peritonitis but because too little is paid to acute appendicitis while it is still acute appen dicitis Appendical peritonitis develops because physi cians fail to recognize the syndrome of uncomplicated appendicitis the spreading of the gospel of which has been Bower s chief contribution to the subject

The appendix is a vestigial organ It is a blind pouch which may assume various positions in relation to the cecum It has a terminal blood supply and an obstruc tive mechanism at the base It is filled with infected contents even under normal circumstance and it con tains a large amount of lymphoid tissue which is notoriously prone to infection These facts all make

(2) South M & S 103 588 94 Novembe 1941

clear the reasons why, when once disease has been initiated the circumstances are all in favor of its assuming a progressively serious course

The problem of acute appendicitis would be solved *and its challenge met if the laity could be taught and* if physicians would remember (1) that any abdominal pain may be the first symptom of acute appendicitis (2) that food fluids and particularly purgatives should be withheld in every case of abdominal pain until acute appendicitis has been excluded as a diagnosis and (3) that prompt operation is indicated as soon as the diagnosis is made or is suspected with good reason

Appendicitis—A Hazard of Youth Dorothea H Scoville[3] (Connecticut College) reviews the mortality rates for appendicitis and points out that the low college death rate indicates that health programs are construc

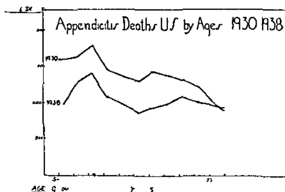


Fig 166

tive As for the disease itself it is more common among men than women and most common between the ages of 10 and 30 Some of the predisposing factors are stagnation of the intestinal contents in the appendix resulting in formation of hard concretions which may

(3) J rn l La et 61 457 46 N mb 1941

set up inflammation habits of life particularly dietary involving excessive food consumption or an overindulgence in certain types of food especially low residue pap foods increasing and indiscriminate use of laxatives and cathartics and inadequate physical exercise and a sedentary life

APPENDICITIS DEATHS BY AGE GROUPS

1930*		1938†	
Age Group	No Deaths	Age Group	No Deaths
Under 5	885	Under 5	676
5-9 yrs	1 520	5-9	954
10-14	1 543	10-14	1 237
15-19	1 696	15-19	1 344
20-24	1 425	20-24	1 030
25-29	1 290	25-29	934
30-34	1 237	30-34	823
35-39	1 347	35-39	895
40-44	1 281	40-44	949
45-49	1 245	45-49	1 069
50-54	1 181	50-54	985
55-59	949	55-59	972
60-64	833	60-64	850

* Mortality Statistics 1930 31st Annual Report U S Dept. of Commerce Bureau of the Census (Washington 1934) p 248 table 7
† Vital Statistics Special Reports Deaths from Each Cause [illegible] Dept of Commerce Bureau of the Census (Washington [illegible] 1940) Vol 13 no. 51 p 648

The most complete campaign to lower appendicitis death rates has been made by Bower of the Philadelphia General Hospital The appendicitis mortality percentage in Philadelphia dropped from 5 97 per cent in 1929 to 3 44 per cent in 1932 Bower attributed this to the intensive educational campaign among the doctors and the public and lists the following factors (1) a marked *increase in the number of cases over preceding years* (2) *earlier hospitalization* (3) *diminished number of cases of peritonitis* (4) *diminished number of cases of spreading peritonitis* (5) *improvement in management of spreading peritonitis by the surgeons of Philadelphia* and (6) less frequent administration of laxatives If

similar efforts were made throughout the country some 9 600 lives might be saved annually in the United States

Role of the General Practitioner in Appendicitis Royal A Schaaf[4] (Newark) states that there has been little diminution in the mortality and serious postoperative morbidity of appendicitis in the past 25 years mainly because of (1) delay by the patient and (2) delay by the medical or surgical attendant Delay by the patient is caused by ignorance poverty self medication lack of available surgical aid etc Vigorous and continued campaigns to educate the laity are a vital necessity

The pathologic changes in suppurative and gangrenous types of appendicitis are essentially dissimilar Suppurative appendicitis is in effect a cellulitis of the coats of the appendix progressing to suppuration Gangrenous appendicitis is primarily a gangrene of the appendix with secondary suppuration the gangrene being caused by thrombosis of the appendical vessels resulting from their injury by fecaliths overdistention or other mechanical causes followed by infection In the suppurative type elevation of temperature appears early In the gangrenous type a rise may not occur until many hours later after secondary infection has begun Thrombophlebitis of the portal tributaries occurs mostly in cases of gangrenous appendicitis The only constant symptom of appendicitis is abdominal pain but its point of origin location radiation severity and character vary greatly Absence of vomiting and nausea must not rule out appendicitis The temperature must always be taken rectally elevation of temperature may be slight in elderly or debilitated persons Great reliance may be placed on an accurate Schilling count showing a marked shift to the left but the total count often fails to indicate the severity of the inflammatory process again especially in elderly or debilitated persons

(4) J M Soc N w J y 39 76 79 F bru ry 194

Errors in diagnosis occur most frequently in cases in which the cecum or appendix is abnormally placed These organs may be situated well up in the right upper quadrant where appendicitis will simulate gallbladder disease They may be in the pelvis thus leading to the diagnosis of rectal bladder or genital inflammation They may be transposed or if the mesentery is long may gravitate to the left iliac fossa The appendix may be retrocecal with a point of tenderness in the loin leading to an erroneous diagnosis of kidney stone or of pyelitis Incorrect diagnosis may be given because of the age of the patient Appendicitis occurs much more frequently in old persons than is generally appreciated, and the proportion of diagnostic errors in this group is correspondingly high In elderly persons appendicitis is frequently insidious in onset causing only moderate pain slight elevation of temperature and indefinite local signs The true nature of the condition may not be apparent until a palpable mass develops in the right lower quadrant The total leukocyte count may not be increased It may even be diminished but an accurate Schilling count often solves the problem On the other hand in children the disease develops rapidly and correct diagnosis is of greatest importance The adage In children abdominal pain with vomiting means appendicitis until it can be positively excluded should be remembered Careful rectal examination is required Despite common belief presence of chills does not rule out appendicitis When they do occur ligation of the appendical or ileocolic veins must be done to prevent pylephlebitis with secondary multiple abscesses of the liver Incorrect diagnosis may also be given because the appendix is acutely obstructed by a fecalith or a mechanical kink in the orifice of the appendix permitting gas to enter but not to escape The appendix becomes distended and in effect there is intestinal obstruction limited to the appendix Onset of pain is always in the epigastric region is severe and is accompanied by

persistent vomiting poor response to enemas and little or no elevation of temperature Diagnosis hinges on tenderness in the right iliac fossa with a marked shift to the left in the Schilling count Appendicitis may follow onset of pneumonia especially in children Such cases present the greatest diagnostic difficulty but persistent vomiting with right lower quadrant pain and tenderness calls for closest observation and occasionally exploratory incision

If finally after careful observation and study the diagnosis is still in doubt it is better to operate even though operation may show a normal appendix

Intestinal Obstruction from the Practitioner s Point of View W Osler Abbott (Univ of Pennsylvania) states that from the standpoint of the general practitioner intestinal obstruction is no longer a diagnosis that need carry with it the implication of an emergency *operation Means are available today for correcting* and maintaining nutrition without utilizing the digestive tract means are likewise available for emptying the gut proximal to the obstruction without incising it As these changes have made treatment of obstruction less routine they have made prompt diagnosis of strangulation more urgent for it is almost as grave an error to perform an emergency operation on an unprepared patient in the absence of strangulation as to delay operation when the blood supply of the gut is in jeopardy

Three points are of great usefulness in establishing a diagnosis of strangulation First a patient with simple obstruction is doubled up by intense pain coinciding with waves of colic which are often audible without a stethoscope and not infrequently palpable or visible through the abdominal wall With the passage of the wave there is little evidence of distress until the next colic grips The patient with strangulation however will have the same severe waves of pain but between these waves there is no relief from pain This persistent

(5) N w Y k St t J M d 4 4 1 4 4 M 1 1942

Errors in diagnosis occur most frequently in cases in which the cecum or appendix is abnormally placed These organs may be situated well up in the right upper quadrant where appendicitis will simulate gallbladder disease They may be in the pelvis thus leading to the diagnosis of rectal bladder or genital inflammation They may be transposed or if the mesentery is long may gravitate to the left iliac fossa *The appendix may be retrocecal with a point of tenderness in the loin leading to an erroneous diagnosis of kidney stone or of* pyelitis Incorrect diagnosis *may* be given because of the age of the patient Appendicitis occurs much more frequently in old persons than is generally appreciated, and the proportion of diagnostic errors in this group is correspondingly high In elderly persons appendicitis is frequently insidious in onset causing only moderate pain slight elevation of temperature and indefinite local signs The true nature of the condition may not be apparent until a palpable mass develops in the right lower quadrant *The total leukocyte count may not be increased It may even be diminished but an accurate Schilling count often solves the problem* On the other hand in children the disease develops rapidly and correct diagnosis is of greatest importance The adage In children abdominal pain with vomiting means appendicitis until it can be positively excluded ' should be remembered Careful rectal examination is required. Despite common belief presence of chills does not rule out appendicitis When they do occur ligation of the appendical or ileocolic veins must be done to prevent pylephlebitis *with secondary multiple abscesses of the liver* Incorrect diagnosis may also be given because the appendix is acutely obstructed by a fecalith or a mechanical kink in the orifice of the appendix permitting gas to enter but not to escape The appendix becomes distended and in effect there is intestinal obstruction limited to the appendix Onset of pain is always in the epigastric region is severe and is accompanies If

Role of Roentgen Examination in Diagnosis of Intestinal Obstruction Correct interpretation of observations obtained from careful roentgen examination of the abdomen or the gastro intestinal tract is the most valuable aid in the diagnosis of intestinal obstruction Patients with obstructive lesions in the intestinal tract do not always present classic symptoms and diagnosis can be made only from a roentgen study *Eugene P* Pendergrass[6] (Univ of Pennsylvania) recommends fluoroscopic study in the horizontal and semierect positions provided the patients with an acute abdominal condition can be moved The advantage of fluoroscopy is that the extent of the movement of the domes of the diaphragm can be determined and roentgenograms made of the important fluoroscopic observations

The minimum requisite of such a study is a film of the abdomen in the anteroposterior position Additional films which may give valuable information are postero anterior and lateral films in the recumbent position anteroposterior or postero-anterior films with the patient lying on the left or right side and anteroposterior or postero-anterior films in the erect position The shadow of the domes of the diaphragm should be included on the film and a lateral view of the pelvic region should be available for study of gas shadows in the rectum. The purpose of the survey is to determine the presence and location of any demonstrable gas in the intestinal tract or abdomen the presence or absence of muscle shadows and the preperitoneal fat lines and the possible location of any abnormal soft tissue lesions

Under normal conditions gas shadows are usually not seen in the small intestine but are frequent in the stomach and colon Abnormal gas shadows in the small intestine and colon may be produced by intestinal obstruction morphine and other sedative drugs peritoneal irritation from any cause such as retroperitoneal

(6) N w E gl nd J M d 25 637 641 O t 3 1941

severe ischemic pain is characteristic of strangulation Second strangulation is associated with far more superficial tenderness and there is a far greater tendency for the tenderness to be localized to some particular area of the abdominal wall than is the case in obstruction without strangulation Finally, the waves of peristalsis which cause pain in the absence of impaired blood supply can generally be inhibited by administration of 1/6 gr morphine sulfate subcutaneously, and with cessation of contractions there is an end of colic at least for some time The patient with strangulation however rarely obtains complete relief from a single dose of this size

If strangulation is definitely not present the alternative to immediate operation is decompression by intestinal intubation and correction of nutritional defects by intravenous alimentation For decompression a special double barreled tube with a thin rubber balloon at its tip is used The tube is advanced until it reaches the obstruction and remains there Constant suction draws off the intestinal contents and the residue of the food The doctor then waits for one of two developments that depend largely on the nature of the lesion The patient s metabolic state is brought into balance and then when well prepared he is either operated on or the obstruction is permitted to subside The latter occurs with astonishing frequency The mechanism of the relief is related to the nature of obstructions in general They are frequently the result of three changes in the gut wall (1) anatomic narrowing due to angulation tumor or fibrosis (2) local inflammatory reaction and (3) nutritional edema The anatomic change is unaltered by conservative treatment the local inflammation is relieved by sustained decompression of the proximal segment and the hypoproteinemic edema is decreased by improved nutrition. The result will often be a disappearance of all evidence of obstruction

tion than a lesion of the small intestine and the cecum is more vulnerable to distention than other portions of the colon Films made in the erect and lateral decubitus positions demonstrate any free gas in the peritoneal cavity Thick shadows of the intestinal walls may be due to peritonitis Loss of the shadow of the preperitoneal fat line or absence of the lumbar muscle shadows should be noted because such signs may indicate peritonitis

The procedure of intestinal intubation in obstruction consists in the passage of the tube down the intestine until it stops or if the obstruction is paralytic until the obstruction has been overcome In mechanical obstruction a thin suspension of barium is injected to determine the presence of an intrinsic lesion (tumor) or extrinsic lesion (adhesions) If after injection of the barium the opaque suspension regurgitates proximally along the barrel of the tube an obstructive lesion is suspected Colonic lesions are likely to cause the tube to stop progressing in the small intestine in the right iliac fossa owing to spasm of the ileum A barium enema is required to diagnose or exclude a colonic lesion before making a diagnosis of an organic ileal obstruction When using the Miller Abbott tube evidence of pleating of the tube proximal to the balloon must be looked for the patient should continue to swallow the tube until pleating has disappeared before it can be ascertained that the tip will not retreat up the intestine on deflation of the balloon

Multiple obstructions usually fall into several categories multiple obstructions of the small bowel due to adhesions or metastatic cancer those of the small and large bowel caused by tumors those of the small intestine and colon due to effects of irradiation those of the small and large bowel due to an inflammatory lesion or granulomas such as regional ileitis those of the colon due to a tumor and an inflammatory process elsewhere such as diverticulitis If intubation is used the

hemorrhage caused by an injury dysentery and many bacterial and chemical irritants and nutritional deficiencies ruptured graafian follicle, and conditions such as diabetes and sickle cell anemia

The emptying time of patients with reconstructive *gastric operations may be considerably delayed thus* possibly giving rise to a false diagnosis of mechanical obstruction due to adhesions or some defect resulting from the operation This slower emptying time is caused by operative trauma hypoproteinemia and possible vitamin deficiencies conditions which usually correct themselves after a certain time If such factors account for the patient s symptoms and are recognized an unnecessary operation may be prevented

If the gas shadows are limited to the colon and the symptoms are acute the obstruction is usually found in that organ The small bowel rarely participates in a colonic obstruction unless the process is chronic and extends beyond the confines of the colon or unless the lesion is associated with a spreading infection If the abnormal gas shadows are limited to the colon the obstruction is likely to be mechanical Signs helpful in making a diagnosis of volvulus of the sigmoid flexure include the increased size of the flexure most of the lumen of which is found high up in the abdomen outside the pelvis and to the right of the midline presence of unusual amounts of fluid and demonstration of a double point of obstruction A barium enema may be necessary and is best given in the knee chest position If the patient has a primary lesion of the colon such as diverticulitis or an infected carcinoma the small intestine as well as the colon is frequently distended A stethoscope assists in diagnosing or excluding a paralytic ileus and a barium enema may help to determine the nature of the pathologic process especially when the gas shadows of the small intestine simulate the haustral markings in the colon

A colonic lesion is more likely to result in perfora

distention tends to be limited to the right side of the abdomen A corrugated appearance of the anterior ab dominal wall *and movement of peristaltic waves in* patients (not obese) indicate a chronic obstruction be cause of the hypertrophy of the muscle of the normal muscular coats of the intestinal loops Palpation of the abdomen should determine the presence of an abnormal mass the presence of hernia and whether or not perito-neal irritation is present Determination of the presence extent and degree of any peritoneal irritation is ex tremely important On the basis of this part of the examination alone the physician is often forced to decide whether strangulation exists Tenderness re *bound tenderness and muscle spasm must be sought for* and considered Unless there is a satisfactory explana tion of these findings on other grounds their existence in cases of obstruction must always be taken to indicate strangulation Some patients with a moderate degree of peritoneal irritation may have only simple obstruction and thus be subjected to operation under a mistaken diagnosis of strangulation This should not deter the surgeon from operating without delay in all cases with definite peritoneal irritation Auscultation of the ab domen is important and should take at least 15-20 min utes Rectal *and vaginal examinations are important to* detect masses within the pelvis which may either be the cause of the obstruction or be produced by it Distended fluid filled loops of intestine may occasionally be pal pated Strangulated blood filled coils of gut can be felt more definitely A carcinoma of the rectum causing obstruction can often be directly palpated In cases with intussusception rectal examination may reveal the doughnut like intussuscipiens as an intracolonic mass In other cases with the same condition though no mass is felt blood can be seen on the examining finger

Special diagnostic procedures include laboratory tests and x ray examinations Diagnosis should not be made on x ray findings alone but the films should be consid

radiologic diagnosis of multiple obstruction may be made on the basis of the following observations The Miller Abbott tube may fail to progress beyond a certain point and gas distended loops of small intestine may be present beyond the tip of the tube, the tube may not go beyond the left lower quadrant with either gas-distended loops of small intestine distal to the tip of the tube or a distended large bowel or both, and there may be obstruction to the injected barium, together with obstruction demonstrable by a barium enema

Diagnosis of Intestinal Obstruction John R Paine (Univ of Minnesota) states that the diagnosis must include information on (1) the approximate point of obstruction (2) the degree of obstruction, (3) whether the obstruction is simple or strangulating and (4) the pathologic condition responsible for it Only patients with strangulating or complete obstruction of the colon demand immediate operation Others can be satisfactorily controlled for hours or days by constant suction applied to an indwelling tube to gain time to restore the physiologic status of the patient to near normal by parenteral injection of saline and glucose solutions or by blood transfusions. Such treatment during the preoperative period decreases the risk of operation and the resultant mortality

The medical history should include the age of the patient nature and extent of previous abdominal operations duration of present illness character of onset of symptoms character of abdominal pain frequency of vomiting and character of vomitus presence of audible intestinal noises passage of feces and gas and recent loss of weight and strength The general physical examination must be done with care and attention to small details Inspection of the abdomen will reveal the degree of distention, which is less in lesions high in the jejunum and greatest in lesions of the ileum or colon. If the obstruction is in the transverse or ascending colon, the

(7) Am J Surg 56 87 93 Ap 1, 194

the ileum which had caused intussusception of the ileum into the ascending colon His only complaint was pain in the right lower abdominal quadrant Of the 10 patients whose only indication of tumor was loss of blood 8 gave a definite history of tarry stools The value of hemoglobin of the other two patients was 5 5 and 5 8 Gm per 100 cc blood The stools of these patients contained occult blood

CLINICAL MANIFESTATIONS IN 35 CASES OF TUMORS OF THE SMALL INTESTINES

Manifestation	Cases
Loss of blood only	10
Loss of blood and mass	8
Loss of blood mass and obstruction	5
Loss of blood and obstruction	3
Mass alone	3
Mass and obstruction	2
Obstruction alone	
No manifestations	[illegible]
Total	35

Loss of blood was [illegible] by [illegible] of hemoglobin [illegible] 12 Gm per 100 cc. blood and/ [illegible]

Ten patients were operated on without complete roentgen examination of the small intestine For three of these diagnosis of intestinal obstruction was made from a roentgenogram of the abdomen made without use of contrast material An abdominal mass was present in each of the other seven patients The gastro intestinal tract of the remaining 25 was studied roentgenographically with contrast material In each case examination included that portion of the small intestine in which the tumor later was located The lesion was demonstrated in 22 cases and overlooked in 3 Such tumors usually are manifest roentgenographically by producing obstruction by causing intussusception and by producing a filling defect Only in the last instance is it possible to obtain sufficient information to enable the examiner to attempt a definite pathologic diagnosis For this reason various diagnoses were made in the 22 cases in which

ered a means of confirming the results of physical examination and of excluding other possible diagnoses The scout film with the patient prone is the most valuable film

Clinical and Roentgenologic Manifestations of Tumors of the Small Intestine Because of the risk of an increased amount of radiation from repeated roentgen examination of the small intestine patients subjected to such examination must be carefully selected and unnecessary or routine examination must be kept to a minimum To determine a practical basis for selection of patients for examination C A Good and W C MacCarty Jr [8] present a review of 35 cases in which exploration was done primarily because of tumor The most common tumor in this group was adenocarcinoma, with leiomyoma second in frequency

Twenty five of the patients were males The oldest patient was 78 and the youngest 8 months 28 patients were over 40 Eight of the lesions occurred in the duodenum 15 in the jejunum and 12 in the ileum Thirteen of the 16 adenocarcinomas as well as 4 of the 6 leiomyomas were in the upper portion of the small intestine

The most important clinical manifestations were evidence of loss of blood presence of a mass in the abdomen and evidence of past or present intestinal obstruction The table shows the incidence of these symptoms both alone and in combination Loss of blood includes passing tarry stools hematemesis or a value of hemoglobin of less than 12 Gm per 100 cc blood Obstruction includes an easily recognizable history of intestinal obstruction or evidence of obstruction obtained from physical examination Only two patients had none of these three symptoms One was found to have a small polypoid lipoma in the first portion of the duodenum discovered by roentgen examination of the stomach to determine the cause of heart burn The other patient had an annular reticulum cell sarcoma of the terminal portion of

(8) Proc Staff Meet Mayo Clin 17 20 J 14 194

organism. Prior to the introduct on of the sulfonamides, there was no successful germicide for Streptococcus faecalis It is com forting to realize that in sulfathiazole coupled with a suitable pH we have a dependable remedy —Ed]

Preliminary Colostomy in Management of Gastrocolic **and Gastrojejunocolic Fistulas** Carleton Mathewson Jr[1] (Stanford Univ) studied nine cases of gastro jejunocolic fistula four of gastrocolic fistula and three of enterocolic fistula He reports in detail three cases of gastrojejunocolic fistula treated by preliminary colostomy This procedure not only stops the diarrhea imme diately and completely allowing the patient to regain his body weight and normal fluid balance but greatly facilitates surgical correction of the fistula at a subse quent operation by correcting the inflammatory reaction usually seen about these fistulas The diarrhea present in gastrojejunocolic fistula is definitely the result of a reflux of colonic contents into the upper gastro intestinal tract rather than the influx of gastric contents into the large bowel Diarrhea is a symptom of gastrojejunocolic fistula but not necessarily a symptom of gastrocolic fistula Concerning the choice of operations Mathewson recommends right sided transverse colostomy which he has found preferable to cecostomy in such patients Simple restoration of continuity after colostomy is frequently followed by return of the original ulcer symptoms simple closure of the colonic fistula is apt to lead to recurrence Since preliminary colostomy makes any subsequent procedure simpler and safer extensive gastric resection later is permissible

[Without adequate preoperative preparation the mortality makes surgery prohibitive even in the best of hands Conse quently even a surgical procedure such as colostomy as a pre liminary to gastric resect on is highly commendable if life saving —Ed]

Vitamin Deficiencies and the Small Intestine Thomas T Mackie[2] (Roosevelt Hosp New York City) states that characteristic roentgen changes are demonstrable

(1) A n S g 114 1004 1010 D emb 1941
(2) J A M A 117 910 91 S pt 13 1941

a tumor was found roentgenographically Diagnosis of carcinoma was made in five cases, ulcerating malignant disease in one intramural submucosal tumor in five, intussusception in four obstruction in four, polypoid lesion in one and ' lesion in one

Bactericidal Action of Sulfathiazole on the Streptococcus Faecalis H F Helmholz[9] states that clinically there has been much difficulty in eradicating Streptococcus faecalis with sulfanilamide and even with sulfathiazole Experimentally it was shown that the latter drug acted much more effectively at a pH of 5 5 than it did at pH 6 5 or 7 5 It did act bactericidally, however at *pH 6 5 and 7 5 but a greater concentration* of the drug was necessary than at the lower pH Use of sulfathiazole in cases of urinary infections with reduced renal function is of particular interest This reduced function makes the attainment of a low pH and a high concentration of the drug impossible When renal function is normal calcium mandelate will affect all bacteria, but to affect any bacteria it must be present in a concentration of 0 5 per cent and the urine must have a pH of at least 5 5 this the damaged kidney cannot accomplish Helmholz studied the effect of various concentrations of the drug and pH of the urine on Streptococcus faecalis with a large series of organisms namely, 34 strains

The results showed that the growth of the organism in urine is inhibited at a pH of 4 9 The necessity for the low pH for the effective action of low concentrations of sulfathiazole on the organism puts it into a class with methenamine and mandelic acid which have a definite standard value as urinary antiseptics for all bacteria at pH 5 5 Sulfathiazole was found to be definitely superior to sulfanilamide in its bactericidal action on Streptococcus faecalis

[In the past, successful treatment of urinary infections frequently eluded us, especially if the streptococcus was the offending

(9) Proc. Staff Meet., M yo Clin 16 737 744 Nov 19 1941

Appropriate treatment is followed by improvement in the intestinal picture Ross Golden[3] (Columbia Univ) reports observations on the small intestine in a series of more than 100 cases in which some deficiency condition appeared to play either a major or a minor part

The small intestine study consists of a series of roentgenograms of the abdomen taken at approximately *half hour intervals after ingestion of a barium sulfate* suspension in the morning during fasting The suspension consists of 4 oz chemically pure barium sulfate in physiologic solution of sodium chloride made with distilled water The films are developed and inspected immediately and the routine is modified if required Fluoroscopic examinations are made two or three times during the procedure usually with pressure films of the terminal part of the ileum or of other parts if indicated Food is usually given at five hours or earlier if the barium has entered the cecum The series is concluded within five or six hours or sooner if all needed information has been obtained

The abnormalities of the small intestine in deficiency states may show themselves in changes in the motility such as hypermotility hypertonicity hypomotility hypotonicity (dilatation) abnormal segmentation scattering effect and abnormal gas and fluid levels The mucosal folds may be greatly reduced in number or in advanced stages may be completely obliterated giving the wall a smooth appearance With appropriate treatment the mucosal folds reappear The folds may be abnormally wide and irregular in width height and spacing In the earlier stages they sometimes appear as low rounded indentations in the margin of the barium shadow In occasional instances the mucosal folds of the jejunum may appear normal on the first two or three films and then the irregular arrangement appears Similarly the appearance of segmentation may be delayed this has been noted in a typical case of sprue

(3) J A M A 117 913 91 Sept 13 1941

in the small intestine in the presence of deficiency states Since these changes are present in the new born and disappear in the early *months of life and since degenera*tion of the nerve cells of the myenteric plexuses in an adult presenting the deficiency pattern has been demonstrated it is probable that they result from interference with the intrinsic nervous mechanism of the small intestines The deficiency pattern may be produced in animals and man subjected to experimental B complex deficiency When occurring naturally it is accompanied by a high incidence of clinical indications of B complex deficiency If irreversible changes have not occurred, it responds to the therapeutic administration of heavy dosage of the B complex in the form of crude liver extract or yeast It does not respond to thiamine, riboflavin or nicotinic acid and consequently must depend on some factor in the vitamin B complex other than these substances The deficiency pattern is accompanied by interference with the function of absorption and may therefore contribute to the establishment of an ascending spiral of progressing deficiency disease Since it has been observed that these changes vary directly with the severity of the clinical condition and regress to a variable degree under specific therapy they afford a means of evaluating the efficacy of the therapeutic regimen and likewise afford evidence of prognostic significance

Small Intestine in Vitamin B Deficiency The association of abnormalities of the small intestine with nutritional disorders in which vitamin deficiency plays a part has been pointed out by many authors Snell and Camp believed that these abnormalities were probably not characteristic and could be produced by other conditions Continued roentgen study of the small intestine has *shown that analogous changes of varying* degree may be discovered in patients with abdominal symptoms but without the usual clinical manifestations of recognized vitamin deficiencies as well as in patients with recognized visceral disease such as peptic ulcer

3 Gm for two days followed by 4 Gm daily in two doses of 2 Gm. If the diarrhea was not controlled in four days the maintenance dose of 4 Gm per day was continued for one week. Later experience showed that larger doses can be used without causing toxic effects and may be advisable in cases of severe dysentery. A sample of blood was taken into oxalate 24 hours and again 4 days after starting treatment to estimate the level of the drug. A morning specimen of urine was collected on the fourth day of treatment and examined for drug content, protein, crystals, casts and cellular content. White cell counts were made on some treated and untreated patients. All treated patients received a liberal supply of fluids for the period of drug therapy since sulfaguanidine and particularly its acetylated derivative may have irritative and toxic effects on the kidneys.

Treatment with the drug in the acute stage of the infection apparently helped prevent a convalescent carrier state which was present in about half of a bacteriologically controlled untreated group. The drug apparently owes much of its effectiveness as an intestinal antiseptic to its poor absorption from the intestine since one half to two thirds of it remains unabsorbed. Blood and urinary concentration of the drug were low relative to the dosage given and toxic effects were conspicuous by their absence. Since crystalline deposits occur in the urine with concentration over 175 mg per 100 cc an adequate fluid intake and output must be maintained to avoid local toxicity or irritation in the urinary tract; no evidence of any such effect was found in this series.

The use of a new culture medium, desoxycholate citrate agar, resulted in isolation of Bacillus dysenteriae (Flexner) from a high proportion of both typical and atypical infections. Its superiority over MacConkey's medium was most noticeable in the isolation of the pathogen during convalescence. The authors conclude that

after the patient had improved under suitable therapy.

Except in cases of the most advanced severe vitamin deficiency, *appropriate treatment is followed by improvement* in the function of the small intestine, as manifested by roentgen examination. In the more advanced stages mucosal folds reappear on previously smooth jejunal walls, hypotonicity decreases and segmentation gradually diminishes. In the earlier stages the exaggerated irregular mucosal folds become regular and even. Segmentation disappears first in the upper third of the intestine and later lower down. Hypomotility may be followed by hypermotility, particularly of the jejunum, with a subsequent return to normal limits in the rate of movement of intestinal contents. In far advanced deficiency states, complete restoration of the intestine to normal has not occurred.

It seems probable that interference with or damage to *the intramural nervous system is the common mechanism* by which the intestine is affected. Despite the nonspecificity, demonstration of roentgen changes may be in many cases the first suggestion that a vitamin deficiency may play a primary or secondary part in a patient's condition.

Treatment of Bacillary (Flexner) Dysentery with Sulfaguanidine. David E. W. Anderson and Robert Cruickshank[5] (Northwestern Hosp., Hampstead) used this new intestinal antiseptic in the treatment of 41 adults with acute bacillary dysentery with beneficial results, especially in the more severe infections. A series of 55 patients in the same epidemic served as controls.

The drug was given in powder form. It can be introduced as a suspension in water or milk; it has little taste and does not produce nausea or vomiting. At first the prescribed dosage was 6 Gm. daily in three doses of 2 Gm. for four days, but after a preliminary trial this dosage was changed to 9 Gm. per day in three doses of

(5) Brit. M. J. 2: 497-501, Oct. 11, 1941.

3 Gm for two days followed by 4 Gm daily in two doses of 2 Gm If the diarrhea was not controlled in four days, the maintenance dose of 4 Gm per day was continued for one week Later experience showed that larger doses can be used without causing toxic effects and may be advisable in cases of severe dysentery A sample of blood was taken into oxalate 24 hours and *again 4 days after starting treatment to estimate the* level of the drug A morning specimen of urine was collected on the fourth day of treatment and examined for drug content protein crystals casts and cellular content White cell counts were made on some treated and untreated patients All treated patients received a liberal supply of fluids for the period of drug therapy since sulfaguanidine and particularly its acetylated derivative may have irritative and toxic effects on the kidneys

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the combination of an efficient intestinal antiseptic as the present one and a culture medium which will readily detect mild infections and convalescent carriers may be *instrumental in eliminating dysentery from mental* hospitals

Chronic Ulcerative Colitis Lester R Dragstedt, G M Dack and J B Kirsner[7] (Univ of Chicago) present a summary of the problem of chronic ulcerative colitis



Fig 167 —Cha a t r stic m rphology f Bact um ecroph rum pleo-mo ph m nd fil m nt u fo ms × 3 80

and evidence which shows that *Bacterium necrophorum* together with some as yet unknown factors plays an etiologic role in the disease When the seriously diseased colon in patients with chronic ulcerative colitis is isolated from the fecal stream as by end ileostomy aerobic organisms disappear and anaerobic organisms persist in large numbers in cultures secured by swabs or saline washings of the lower sigmoid flexure Since the isolated colon remains diseased for years, it seems probable that the responsible organism or organisms are anaerobic The following evidence indicates that Bacterium necrophorum is of etiologic importance in this disease (1) It is the

(7) An Su g 114 653 66 O tobe 1941

predominant organism in the isolated colon in ulcerative colitis during periods of exacerbation and tends to disappear during periods of spontaneous quiescence (2) It has been found in most cases of typical ulcerative colitis when appropriate methods for its detection have been used (3) Specific antibodies for this organism have been found in the blood of patients with chronic ulcerative colitis and not in the blood of normal persons (4) The organism is pathogenic for rabbits producing in them local abscesses and for man as indicated by its isolation in pure culture in a wide variety of pathologic processes (5) Examination of the literature indicates that it is similar to if not identical with Bacillus or Bacteroides funduliformis which has been repeatedly found associated with necrotic lesions of the mucous membranes in man and with Bacillus necrophorus which is thought to cause various necrotic lesions in domestic animals



Fig 168 —A b blood g pl t from w b lt t k n t p oct sc p f m ut ly ul t d f ol n p t t w th h n l t l t l with d k g B t m ec ph m

Bacterium necrophorum is probably present in the normal alimentary tract of man and monkeys and requires some additional factors producing necrosis of the mucosa to furnish conditions suitable for its growth Once this occurs the organism seems capable of continuing and extending the process

Diverticulosis and Diverticulitis The investigation reported by Hugh R G Poate[6] (Prince Henry Hosp Sydney) indicates that diverticula of the colon are of

common occurrence and, being narrow necked, thin walled hernias of mucous membrane covered by peritoneum beneath which there may be variable amounts of fat, they are liable to cause various troubles if inflammation sets in The etiology is probably a summation of several factors acting on an area of bowel wall where some muscular weakness has developed in relation to the site of entry of the blood vessels The principal factors precipitating acute diverticulitis include straining at stool, use of harsh cathartics enemas given with excessive pressure and strenuous exertion Foods which irritate the colon or increase its bacterial content may be contributory factors Diverticulitis may lead to other complications Perforation abscess formation or peritonitis is more likely to occur in younger persons while chronic obstructive lesions are more likely to occur in the older age groups being due to a low grade infection permeating the wall of the diverticulum and extending along and through the wall of the colon The bowel wall may become grossly thickened and simulate a carcinoma closely

Diverticulosis in itself causes no symptoms but if associated with a spastic colon or other form of chronic colitis the usual chain of symptoms incident to these conditions is present With onset of diverticulitis the clinical picture changes and varies according to the acuteness of the inflammation as to whether perforation of the diverticulum occurs or what nearby viscera are involved The most common cause of pain in the left iliac fossa in patients over 40 is diverticulitis of one form or another The younger the patients the more likely they are to develop acute surgical complications which have a high mortality if subjected to immediate operation Although the frequency of diverticulitis is slightly more in the male than in the female the incidence of surgical complications is nearly double in the male If acute complications arise it is best to postpone operation to as late a stage as possible and to disturb the existing

status as little as possible It is better to tide the patient over an acute emergency and to leave any curative surgical procedures until such time as they can be carried out deliberately and under the best possible conditions

The incidence of carcinoma with diverticulitis is incidental rather than actual but the chronic sclerosing diverticulitis may be difficult to differentiate clinically from carcinoma

Unclassified Type of Ulcerative Disease of the Colon Philip W Brown Louis A Buie and Harry M Weber[8] (*Mayo Clinic*) *report on 41 cases in which a diagnosis* of ulcerative disease of the colon of the unclassified type was made Diagnosis was based on proctoscopic roentgenologic and clinical findings which did not fit any known type of ulcerative colitis This group has thwarted the efforts of the clinician roentgenologist and proctologist. The regularity with which the last two have agreed in their confusion is a convincing proof of the enigmatic character of the problem. In about 20 per cent of cases proctoscopic examination reveals nothing of significance However all data indicate that there is a lack of features by which a more exact diagnosis can be made

Treatment consists of a high protein diet with vitamin supplements Good hygiene is essential and the patient must be made to understand that fatigue physical nervous or mental exposure or any form of dissipation of vital resources must be avoided In the records of nearly all patients was a history of over doing in one or more ways that tended to exhaust their vitality Amebiasis must be disproved by a trial therapy by emetine hydrochloride parenterally or treparsol or carbasone orally This avoids the embarrassment of treating a patient conscientiously for months for colitis only to hear of a prompt cure elsewhere with antiamebic treatment The sulfonamide compounds did not produce any impressive results. Iron

(8) South M J 35 305 312 M ch, 194

given orally is often indicated but nearly as often it will increase the diarrhea Parsley has been found *to be one of the richest natural sources of iron, and* patients are told to eat a third of a cupful of chopped parsley three or four times a week It may be eaten as is or flavored with any oil or salad dressing that is agreeable

Histoplasma Capsulatum as Cause of Chronic Ulcerative Enteritis Richard G Henderson Henry Pinkerton and Louis T Moore[9] (St Louis Univ) report a

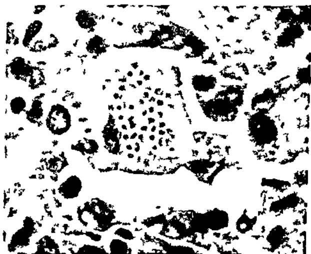


Fig 169 —Parasitized macrophages at base of ulcer in ileum characteristic clear halo around dark staining nucleus × 1 000

case, thus adding 1 to the 30 cases of human infection with Histoplasma capsulatum reported in the literature

Man, 70 complained of persistent diarrhea loss of weight and progressive weakness Severe diarrhea had developed during early harvesting of corn five months before admission Shortly after symptoms began amebas were supposedly found in the stools but diarrhea continued despite treatment He passed 10 to liquid or semiliquid stools daily, which were white and contained soft yellow lumps There were no pain, cramps or blood

(9) J A M A 118 885 889 M 14 194

On admission temperature was 97 F pulse 96 per minute and blood pressure 80/65 The abdomen was distended and slightly tender The liver was palpable and slightly tender Temperature remained subnormal until the evening before death when it was 102 8 F Pulse dropped to 60 per minute and varied between 60 and 80 Urine showed 1 plus albumin with 12 pus cells per high power field Total white cell count was 11 200 cells per cu mm with 2 juvenile cell 9 stab cells 78 segmented forms and 12 lymphocytes The red blood cell count was 3 850 000 Nonprotein nitrogen was 50 mg per 100 cc and the blood sugar was 115 mg



Fig 1 0—T be l lk l w th g t ll
jl n 00

Treatment was only supportive Rectal examination however, disclosed dilations of the rectal pouch with extreme tenderness The day after admission the patient complained of tenderness in the right upper quadrant for the first time He died quietly three days after admission Clinical diagnosis was ulcerative colitis of undetermined cause Amebic dysentery and obscure malignant condition were also considered as possibilities

Microscopic examination of the intestinal ulcers found at autopsy in the terminal ileum cecum and colon showed erosion of the mucosa and submucosa the muscularis remaining intact except in perforated lesions There was a base of granulation tissue in which numerous parasitized phagocytes were found (Fig 169) An occasional mucosal epithelial cell contained parasites The cellular reaction surrounding the ulcer was granulomatous Chronic inflammatory cells were

found along the base of the mucosa away from the ulcera tions *The adrenals showed five to six tubercle like lesions*, somewhat resembling caseous tuberculosis Mesenteric lymph nodes showed circumscribed tubercle like lesions with little necrosis There was generalized reticulo endothelial hyper plasia Many small tubercle like lesions were in the spleen and liver (Fig 170) They contained a central core of epitheli oid cells with a peripheral ring of fibrous tissue Histo plasmas were rare in these lesions, but in the giant cells and epithelioid cells definite vacuoles were found corresponding in size with the yeast bodies some showing bits of degenerating nuclei

The parasite found was identical with the organism de scribed by Darling, with exception of variation in size The *organisms in the intestinal lesions were extremely small* with eccentrically placed nuclei, while the organisms in the adrenal lesions were larger and had centrally placed nuclei There appeared to be an increase in the capsular size with the in crease in size of the organism

Review of the literature shows that 8 of 25 cases available *for analysis showed a similar involvement* but that in only 2 there had been a similar history of severe prolonged diarrhea The almost constant in volvement of the mesenteric lymph nodes would sug gest the gastro intestinal tract as the portal of entry Experimental attempts to infect dogs and guinea pigs by the intratracheal route have been unsuccessful

Carcinoma of the Colon and Rectum Charles W Mayo and Carl P Schlicke[1] (Mayo Clinic) present a clinicopathologic study of 334 cases of carcinoma of the colon and rectum Regional or distant metastases oc *curred in 60 5 per cent* and local *invasion in 39 2 per* cent Among cases in which there was hepatic metas tasis no correlation could be found between the site of the primary tumor and the site of involvement in the liver

The ability of the surgeon to detect metastasis at operation was found to be good *Among cases in which* death occurred shortly after resection, no metastasis was found at autopsy in 82 4 per cent of those which

(1) Surg Gynec. & Ob t 4 83 91 J uary 1942

showed none at operation The success of extirpation was revealed in this same group 65 per cent of those in which there was metastasis at operation being free *of it at autopsy Residual cancer was found in only* 5 3 per cent of the cases in which death occurred shortly after resection Of those cases in which the surgeon believed metastatic growth to be present in the liver the pathologist confirmed the impression in 91 7 per cent

Independent growths are felt to be responsible for many recurrences Polyps were present in 34 1 per cent of the cases in the series in contrast to 16 per cent of a control series consisting of patients without cancer of the bowel In 14 per cent of the cases in which polyps occurred malignant changes were found in the polyps Multiple carcinomas were found in 8 4 per cent of the cases Among cases in which resection was carried out additional independent cancers were found at autopsy in 4 1 per cent Whenever a carcinoma of any portion of the colon or rectum is found the presence of a second carcinoma must be carefully ruled out After operation the malignant potentialities of the remaining mucous membrane should be borne in mind and careful follow up studies carried out

Supplementary and Synergistic Action of Stimulating Drugs on the Motility of the Human Colon The functional motor activity of the canine and human colon can be best described as being propulsive or non propulsive Harry F Adler A J Atkinson and A C Ivy[2] (Northwestern Univ) report that data obtained in 70 control *studies on* four human subjects with colostomy show that the propulsive motility in the distal colon constitutes on the average about 10 per cent of the total motility This value is similar to that obtained in four dogs the average being about 13 per cent The effects of single drugs and their combination were analyzed for the extent of change in the

(2) Su g Gy e. & Obst 74 809 6 0 Ap il 194

two types of functional activity All solutions were given intramuscularly the tablets were given by mouth

Pituitrin in the relatively small dosage of 1 to 2 units caused an increase in the propulsive motility of the human distal colon but did not on the average increase the total motility above the control In the dosage used its action usually did not last longer than 20 minutes The action of pituitrin on the colon of the unanesthetized trained dog with appendicostomy was opposite to that on the human colon Doses of 1 2 or 5 units invariably depressed motility and some times tonus manifest for 30 minutes to several hours the distal colon being more affected than the proximal

Physostigmine sulfate in doses of 1 mg increased the total and propulsive motility of the canine and human colon The simultaneous injection of 1 to 2 units pituitrin and 0 7 to 1 mg physostigmine sulfate resulted usually in a supplementary action on the human colon In three subjects the pituitrin acted first increasing propulsive motility and was followed by physostigmine action which increased both propulsive and nonpropulsive motilities In one subject there was an apparent synergistic action because in three of six instances 1 mg physostigmine when injected alone elicited no definite colon response Prostigmine methylsulfate in doses of 0 25 mg was about equal in its action to 0 5 mg physostigmine on the motility of the human and canine colon The 0 25 mg dose was not effective in all experiments When the dosage was increased to 0 5 mg effective propulsive motility resulted in all cases The nonpropulsive motility was also increased No side effects were noted with either of the foregoing dosages in dog or man

Prostigmine bromide tablets 15 mg given orally to the four human subjects resulted in increase in total and propulsive motility during the experimental time (150 minutes) on only five occasions In 10 experiments increased expulsion of colon material occurred

5 8 hours after administration In one instance there was no effect The simultaneous injection of prostigmine methylsulfate (0 25 mg) and pituitrin (1 25 units) resulted in increase of both types of motility of the human colon The pituitrin in this dosage initiated propulsive motility which lasted about 20 minutes then the prostigmine action appeared and usually lasted several hours In one patient synergistic action apparently occurred since in all cases when the two drugs were injected simultaneously the response to prostigmine was definite whereas in the experiments with 0 25 mg prostigmine methylsulfate alone it was not definite

Injection of ergotamine tartrate (0 25 mg) intramuscularly or 1 tablet (1 mg) by mouth had no discernible effect on the colon of the four human subjects The simultaneous injection of ergotamine tartrate and prostigmine methylsulfate resulted in potentiation of the prostigmine Both nonpropulsive and propulsive motilities were increased above that initiated by prostigmine alone Ergotamine tartrate in tablet form and prostigmine bromide in tablet form given simultaneously resulted in strong propulsive motility in from one to several hours later Duration of action was not longer than that of 15 mg prostigmine bromide alone but the greater efficiency in initiating propulsive motility which evacuated colon contents was evident Simultaneous intramuscular administration of ergotamine tartrate prostigmine methylsulfate and surgical pituitrin resulted in propulsive motility within a few minutes due to pituitrin action and the subsequent continuation of strong propulsive motility attributable to the potentiation of prostigmine by ergotamine Physostigmine sulfate prostigmine methylsulfate and the combinations of prostigmine with ergotamine and pituitrin facilitated the gastrocolic reflex to a meal ingested several hours after administration of the drugs

A combination of ergotamine tartrate (0 25 mg), prostigmine methylsulfate (0 25 mg) and pituitrin (1 25 units) should prove to be more effective in the management of postoperative distention than any of the drugs alone On the basis of duration of action, the absence of side reactions with doses effective in producing strong propulsive motility prostigmine is ranked as the best single drug investigated

[These are observations of practical therapeutic import in a field in which there is much room for improvement especially in the treatment of ileus and adynamic states in general from whatever cause —Ed]

An Improved Colostomy Outfit George F Archer and Julian G Riley[3] (Atlanta Ga) describe a colostomy outfit designed by a patient

APPARATUS —A wax-coated, thin, flat, rubber washer with a flared inner edge is worn against the abdominal wall One rim of the washer is cut, allowing the ends to be overlapped stitched together and made to fit snugly around the individual colostomy Extra washers of varied sizes are available The colostomy tank is made of wax coated rubber stretched over a metal rim A hole about $1\frac{1}{2}$ in in diameter placed near one edge of the tank receives the colostomy stoma A cellophane bag, $\frac{1}{4}$ or 1 lb size, which may be procured from a 10 cent store, is used The mouth of the bag protrudes through the hole in the back of the tank and is held snugly between the tank and the washer The aluminum front of the tank fits snugly into the tank, and the entire outfit is held in place by two elastic belts that snap onto the tank front The front comes in two sizes The thinner one has a depth of slightly less than 1 in and can

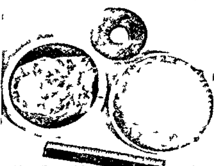


Fig 171 —Unassembled colostomy outfit rubber washer cellophane bag colostomy tank and aluminum front

(3) Surgery 10 83 835 November 1941

be worn when inconspicuousness is essential Gulf wax which can be bought anywhere is used for waxing the washer and the tank. Its melting point is such that at body temperature it is soft enough to form a snug pliable junction. It permits the parts of the colostomy outfit to be cleaned and does not retain fecal odor Each time the bowels move the cellophane bag is discarded the washer rinsed with water and dried and a new bag inserted in the tank.



Fig 172 — [illegible]

The most important advantage of the outfit is that the paper bags can be easily and inexpensively obtained They can with minimum contamination of the fingers, be removed discarded in a water closet and replaced The wearer can continue at work even with a severe diarrhea The use of two paper bags one within the other keeps at a minimum the odor from escaping colostomy gas Wax-coated rubber is easy to clean and does not retain odor A new coating is easily applied by immersing the washer and tank for a moment in melted wax Should the wearer of a bag tank be caught in an afternoon rush crowd he need have no fear that a jostling crowd might cause him to soil himself The tank protects him against blows and the belts hold it securely in place

While taking a bath the wearer can effectively close the colostomy by tying it loosely with a single overhand knot of cotton rope The piece of rope used 1 8 9 in long and is made by rolling between the hands B & B cotton cut ½ in wide with the fiber Such a piece of cotton rope has enough tensile strength to close the colostomy but will not injure the bowel wall It can be used again and again In cleaning a soiled colostomy the material must not irritate the mucous membrane Wet Kleenex or a wet soft toilet tissue serves well for this purpose

DISEASES OF METABOLISM AND NUTRITION

Diabetes Disturbance in Endocrine Regulation of Blood Sugar *Fundamentals of the physiology of diabetes*—Samuel Soskin[4] (Univ of Chicago) states that there are two possible explanations of the diabetic syndrome which results from lack of insulin that were recognized almost from the beginning These are represented by a simple mechanical analogy in Figure 173 *A* indicates the normal state in which the liver furnishes as much sugar to the blood as the tissues draw off The net result of the dynamic balance between inflow and outflow is the normal blood sugar level *B* represents one possible explanation of the diabetic syndrome Utilization by the tissues has ceased while the liver continues to pour sugar into the blood The blood sugar rises until it reaches the renal threshold whereupon glycosuria results The alternate explanation is that there may be no interference with the utilization of carbohydrate as represented in *C* Here the supply of sugar to the blood by the liver has become excessive to the point where continued normal utilization can no longer keep pace with it Thus hyperglycemia and glycosuria can result from overproduction of sugar, even when there is no interference with utilization However the nonutilization theory soon gained the wider acceptance Its acceptance was based on three lines of evidence namely the dextrose nitrogen ratio (D N ratio) the respiratory quotient and ketosis

Minkowski first introduced the D N ratio In analyzing the urine of depancreatized dogs he noted that the ratio of the total sugar in the 24 hour specimen to the total nitrogen averaged about 2 8 1 The D N ratio obtained from dogs treated with phlorhizin under certain conditions is 3 65 1 The glycosuria in the

(4) Northwest Med 40 356 361 October 1941

phlorhizinized animal is accompanied by hypoglycemia instead of the opposite But because in certain cases of severe diabetes mellitus in the human D N ratios were obtained which more closely approximated those obtained in the phlorhizinized dog than those found in the depancreatized dog the higher ratio was adopted for clinical use

Studies of the respiratory exchange of the normal and diabetic organism apparently confirmed the conclusions drawn from the D N ratio The respiratory quotient is the relation expressed in volumes between the oxygen consumed and the carbon dioxide given off The respiratory quotient for oxidation of carbohydrate would be 1 for fat about 0 7 and for protein about 0 8 The quotient of the normal animal under fasting conditions is about 0 7 This has been taken to indicate that fat is the chief fuel being used at that time When however a carbohydrate meal is ingested the quotient rises toward 1 This has been interpreted to mean that the animal is now oxidizing the ingested carbohydrate The diabetic organism differs from the normal in that while the fasting respiratory quotient of the diabetic is also about 0 7 it does not rise when carbohydrate is administered This seems to confirm the fact that the diabetic derives his energy chiefly

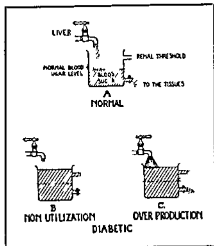


Fig 173

from fat and that he is unable to use carbohydrates

Appearance of the ketone bodies in the blood and urine of the uncontrolled diabetic animal or human was the third basis for the nonutilization theory of diabetes Aceto acetic acid and beta hydroxybutyric acid result chiefly from the breakdown of fat Since these substances did not ordinarily appear in the fasting condition when fat was being metabolized, it was assumed that they were toxic waste products resulting from incomplete oxidation of fats in diabetes From this arose the concept that a certain amount of carbohydrate had to be oxidized so that fats could be burned completely

Present knowledge does not permit acceptance of the nonutilization theory because of a simple but unanswerable objection arising from the experiments of Mann who confirmed the fact that the liver is the chief source of blood sugar Soskin subsequently showed that it is the only source Thus when one removes the liver of a normal animal the sugar continues to be utilized by the peripheral tissues the blood sugar falls steadily and the animal dies in hypoglycemic convulsions in about two hours One might imagine that if the liver were to be removed from a completely depancreatized animal which was supposedly not utilizing carbohydrate no hypoglycemia would result However, Mann demonstrated that when the liver of a depancreatized animal is removed the blood sugar level falls just as rapidly as in a hepatectomized normal animal Unless one makes the rather absurd assumption that removal of the liver suddenly restores the ability of the peripheral tissues to oxidize carbohydrate it must be concluded that the diabetic animal was oxidizing carbohydrate all the time but that the supply carbohydrate from the liver had been so great as to mask the actual amount utilized In other words, one must turn to the overproduction theory of diabetes

The shift of emphasis from utilization by the peri

pheral tissues to sugar production by the liver has practical clinical value *It has been long known that* in certain diabetic individuals in whom cirrhosis of the liver has later appeared the diabetes gradually im proved or even disappeared and some of these patients eventually died in hypoglycemia From the point of view of the overproduction theory the explanation is simple The phenomenon is similar to the hepatectomy experiments Another consideration arising from the present point of view is that of remedies for diabetes other than insulin Soskin recalls the vogue in Europe for the use of synthalin which apparently modified the severity of diabetes in many cases however subse quent investigation proved that it did so by poisoning the liver The same result may be accomplished by any liver poison or by any set of circumstances which causes fatty infiltration of the liver It is therefore necessary before using a substance for which thera peutic claims are made to demand evidence that it not only decreases hyperglycemia and glycosuria but also increases the storage of glycogen in the diabetic liver and does not damage the liver

Endocrine Balance in Carbohydrate Metabolism — Samuel Soskin (Univ of Chicago) discusses the influ ence of the anterior pituitary gland on carbohydrate metabolism in detail The influence of the adrenal cor tex is *similar to that of the anterior pituitary some of* the activity of the pituitary is exerted by way of the adrenal cortex The integrated picture of the relation of the pancreas pituitary adrenal cortex and thyroid to carbohydrate metabolism and to each other is repre sented as a mechanical analogy in Figure 174 Here the position of the liver within the surrounding frame may be taken to represent its finely balanced adjustment in supplying just that amount of sugar utilized by the tissues and in ceasing its production of sugar as soon as the blood sugar level rises above normal Insulin is a

(5) N rthwe t M d 40 457 463 D mb 1941

force exerted in one direction, while the anterior pituitary is an equal and opposite force exerted in the other direction The thyroid and adrenal cortex are represented as subsidiary forces controlled by the pituitary but going in the same direction This balance of opposing forces is conducive to a sensitive and fast acting adjusting mechanism Evidently the same effects may be produced in different ways A weakening of the spring representing the pancreas results in diabetes but the same result may be achieved by tightening the springs representing the opposing glands Thus the fact that administered insulin restores the balance and alleviates the diabetes does not necessarily mean that the original disturbance was caused by lack of insulin There may have been a normal amount of insulin present together with an over action of the opposing hormones

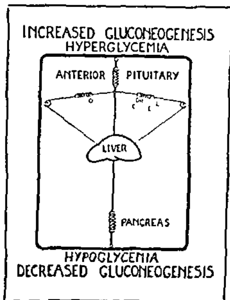


Fig 174.—M han l a alogy f infl e of endoc ne b lance on bohyd ate met bol sm n l r

Obviously the liver is not the only organ concerned with carbohydrate metabolism and with diabetes However some aspects of the function of the liver are relatively little known or only recently discovered furthermore there is no doubt that the liver is the most important organ concerning regulation of the blood

sugar Peripheral tissues particularly muscles play some part in regulation of blood sugar Thus the rate of utilization of blood sugar by the extrahepatic tissues depends on the height of the blood sugar level i e when the blood sugar rises some of the extra sugar present in the circulating blood is disposed of by extra sugar utilization Storage of sugar in both liver and muscles also contributes to blood sugar regulation

Intensive Carbohydrate Therapy in Diabetic Patients with Manifest or Suspected Liver Disease Carl D Strouse E E Rosenbaum Robert C Levy and Samuel Soskin[7] (Chicago) report on two patients with diabetes who developed cholecystitis with liver damage The patients were observed before and after surgical treatment combined with high carbohydrate therapy aimed at treatment of the liver damage One of these cases is given here

Woman 66 was admitted with the diagnosis of acute cholecystitis of two weeks duration She had diabetes for years A year prior to admission she had been taking 24 units of protamine insulin daily On admission she was given a diet of 60 Gm protein 75 Gm fat and 200 Gm carbohydrate together with 25 units of protamine insulin daily On this regimen her daily excretion of sugar varied from 2 to 6 Gm Preoperative treatment included intravenous infusion of glucose for 11 days and similar treatment was continued for 6 days after operation In all she received 1 150 Gm glucose intravenously in addition to her diet before operation and 750 Gm glucose in addition to the routine postoperative diet At operation the gallbladder was found full of pus and stones and cholecystectomy was done Twenty days later she was discharged on a diet of 70 Gm protein 50 Gm fat and 200 Gm carbohydrates without insulin Her urine was entirely sugar free At this time her blood cholesterol which on admission had been 193 mg per cent with 47 per cent esters was 210 mg per cent with 63 per cent esters, and she was clinically well

The dramatic improvement in carbohydrate tolerance which occurred in this and one other patient directed the authors attention to another group of six diabetic pa

(7) J Cl E d 1 1 831 835 October 1941

tients who were exhibiting unexplained loss of carbohydrate tolerance It was suspected that these patients might have subclinical degrees of liver disease Four showed some evidence of mild liver disease and responded to intensive high carbohydrate therapy by a considerable improvement in carbohydrate tolerance Of the remaining two patients, neither of whom gave evidence of liver damage one obtained a favorable result from the treatment while the other did not

Mechanism of Enhanced Diabetes with Inflammation Experiments reported by Valy Menkin[8] (Harvard Univ) show that acute pleural inflammation in a dog fails to alter its blood sugar However an acute inflammatory reaction in a dog rendered diabetic by pancreatectomy induces rapid and marked elevation in blood sugar level The extent of local proteolysis at the site of an acute inflammation in a diabetic dog is considerably more pronounced than that found in a nondiabetic animal This is indicated by a lower concentration of the total proteins and a correspondingly higher concentration of urea nonprotein nitrogen and amino acid nitrogen than is encountered in the exudative material of a nondiabetic animal

The enhanced protein catabolism in the inflamed area of a diabetic animal is correlated with a marked elevation in both exudate sugar and exudate lactic acid Insulin administration not only reduces the level of sugar and lactic acid in such diabetic exudates but diminishes the degree of local proteolysis This fact supports the view that gluconeogenesis at the site of an acute inflammation in a diabetic animal originates from proteins through deamination of the molecule Enhanced local proteolysis in the inflamed area of a diabetic animal implies increased tissue damage The cytologic picture of a diabetic exudate indicates that polymorphonuclear leukocytes manifest pronounced signs of cellular injury when compared with cells from a normal exudate

(8) Am. J Physiol. 134 517 541 October 1941

The biochemical changes encountered in the exudate of a depancreatized dog are similarly reflected in its circulating blood Besides an elevation in blood sugar level there is also an increase in the blood concentration of nonprotein nitrogen urea and amino acid nitrogen Studies after pancreatectomy or splenectomy and a comparison of the relative glucose concentrations in exudate and blood indicate that the raised levels in carbohydrate and nitrogenous constituents of the systemic circulation are due neither to the diabetes per se nor to the operative procedure The elevation in the levels of these substances is referable to an absorption from the area of acute inflammation which complicates the diabetic disorder Insulin by inhibiting glucose formation in the inflamed area likewise prevents a rise in the blood stream of intermediary products of carbohydrate and protein metabolism

The available evidence therefore supports the view that the mechanism of enhanced diabetes with concomitant inflammation might well be referable primarily to an increased local proteolysis in the inflamed area favoring a combined picture of increased tissue damage with a corresponding elevation in glucose formation the glucose in turn gradually diffuses into the systemic circulation

Action of Globin Insulin Compared with That of Crystalline Unmodified and Protamine Zinc Insulin Garfield G Duncan and Charles A Barnes[9] report observations on the comparative effect of equal quantities of unmodified crystalline protamine zinc and globin insulins made on 42 patients the results are reported in 4 diabetic patients and 1 normal control all of whose carbohydrate intakes were uniform throughout the tests. The globin insulin used contains 3 04 mg globin 0 24 mg zinc and 80 units of insulin per cc It is a clear yellowish fluid having a pH of 3 7 Determinations of the blood sugar level were made at intervals of two

(9) Am J M Sc. 0 553 563 O t be 1941

hours In almost all instances the observations were continued until the blood sugar values had risen from the hypoglycemic values to the original fasting levels The observations were repeated at intervals of at least one week until all three insulins were tested

In each instance there was a distinct contrast between the effect of either unmodified or crystalline insulin which begins quickly and is soon ended the effect of the protamine zinc insulin which is delayed in appearance and is prolonged and the effect of globin insulin, which falls between these extremes The blood sugar lowering effect of globin insulin began soon after injection of the insulin and gradually increased in intensity until be tween the eighth and the twelfth hour after injection The effect then gradually subsided The apparent effect of globin insulin in the nondiabetic subject two subjects having mild diabetes and one having severe diabetes persisted for 20 hours after it was injected In one patient having severe diabetes and receiving a larger dose the effect persisted for 24 hours The investigation indicates that globin insulin has a quantitatively greater effect unit for unit than protamine zinc insulin

Efficacy of Intravenous Sodium Bicarbonate Therapy in Treatment of Diabetic Ketosis Louis B Owens Jackson Wright and Edna Brown[1] (Univ of Cincin nati) studied 12 cases of diabetic ketosis to determine the effect of intravenous administration of sodium bi carbonate on the level of blood sugar the carbon dioxide combining power and the level of ketones in the blood and urine early in treatment However, the problem of *death from diabetic ketosis is not solved by correcting* the blood sugar, blood ketones and carbon dioxide com bining power Many patients with ketosis have died though they were chemically cured The mental state of the patient and the duration of mental symptoms have been found to be more closely related to the eventual outcome than have other factors The amount of treat

(1) Arch I t Med 68 1066 1073 Dec mbe 1941

ment, age of the patient presence of circulatory collapse and infection all play a part in recovery These factors were taken into consideration in comparing the mortality for patients treated with sodium bicarbonate with that for patients not so treated to determine whether practical benefit results from its administration

Results showed that intravenous injection of sodium bicarbonate raised the carbon dioxide combining power and relieved Kussmaul respirations but was without effect on the level of sugar in the blood No antiketogenic action was observed but rather a slight tendency in some patients for the elimination of ketones to be delayed

One difficulty in evaluating any single therapeutic factor in diabetic ketosis by the case study method has been the great variation in severity of disease in individual cases Mortality statistics are of little comparative value when one clinic studies a group of unconscious patients who have infection or arteriosclerosis and another studies semiconscious patients in whom ketosis is not complicated *by any other serious factors* When a clinical yardstick such as Rabinowitch s classification is used to estimate the severity of disease much more significant comparison can be made In 47 of 154 cases of diabetes with associated ketosis in which adequate data were available 10 Gm or more of sodium bicarbonate was given intravenously within the first 24 hours of treatment So few deaths occurred in the cases of mild ketosis that the figures are of little comparative value *The mortality for cases of moderately severe ketosis in* which sodium bicarbonate therapy was given was slightly higher than that for those in which this treatment was not used (40 per cent as compared with 33 per cent) The mortality for control cases of severe ketosis was about the same as that for cases in which treatment was given In general the mortality was strikingly similar for the two groups of cases and the authors conclude that there seems to be no practical basis for sodium *bicarbonate therapy in treatment of diabetic ketosis*

Diabetic Coma Elliot P Joslin Howard F Root Priscilla White and Alexander Marble (Boston) state that far better results can be secured by prevention than by treatment of diabetic coma Because treatment with diet insulin and exercise must be carried out daily over years it is imperative that the patient be fully informed regarding his disease In a simple way he must be taught all that is known regarding treatment of the condition and of complications which may arise He must know how to test his urine and must be impressed with the importance of testing it at home at frequent regular intervals He must know how to give his insulin dose accurately and well He must know how to weigh or measure his food and to substitute one food for another and must be impressed with the great importance of following his diet closely Finally he must keep in close touch with his doctor so that from time to time a more detailed estimate of diabetic control may be made and he may be given the benefit of new features in treatment If education of the diabetic patients and their physicians was carried out to its fullest extent the mortality from diabetic coma would approach zero except when a complicating fatal disease is present When a patient is seen in diabetic coma it is proof that somebody has blundered and if death due to diabetic coma occurs the rule still holds

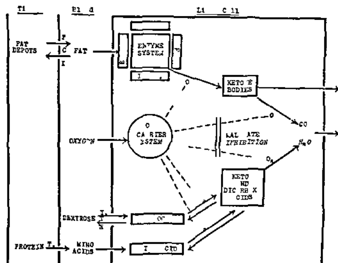
Diabetic coma is an acute deficiency state a condition in which the primary disturbance is a lack of insulin Aids in treatment are (1) large amounts of fluid and sodium chloride to overcome dehydration and electrolyte loss (2) gastric lavage (3) in cases of significant peripheral circulatory failure constant intravenous infusions of salt solution and transfusions of plasma or whole blood in selected patients to restore blood volume Alkalis are not used Dextrose is not given parenterally in early hours of treatment

In 525 cases of coma observed from May 1923 to

(1) J A M A 119 1160 1165 Aug 8 194

January 1942 there were 58 deaths a mortality rate of 11 per cent No death occurred among 62 successive patients treated between August 1940 and July 15 1942

Origin of Ketone Bodies from Fats and Their Regulation The investigation reported by Samuel Soskin and R Levine[3] (Univ of Chicago) indicates that the



F g 1 5—F to fl g t f f m t n f k t b d by l ll *P* t p t t ry f t *C* d l t al f t *I* ul *T* thy d h m n *E* I ph *EFA* f tty d th m b f b t ms *KAA* k t g m n d *Inh b* b t th ct g p m l t th f f tty cid wh b th f h b t k t g by mp t t n f n ym g be d nd alph min b tyr d. M l nat h b t k t g ff t by d c e g mp t t n f a l ble oxyg n n f f t n f tty ac d → k t n b d

ketone bodies are probably normal intermediates of fatty acid catabolism in the liver They appear in excess in the blood whenever the hepatic metabolism of fat is sufficiently speeded up either by a lack of carbohydrate substrate or by a disturbance in the normal regulation

(3) A h I t M d 68 674 686 O t b 1941

of the substrate mixture The ketone bodies are readily utilized by the peripheral tissues under practically all known conditions Further work must determine to what extent the derivation of energy from fat under various conditions proceeds through these physiologically important substances

Hyperinsulinism This term according to Edward H Rynearson[4] (Mayo Clinic) should be reserved for cases in which symptoms can be proved to have been caused by too much insulin Hypoglycemia may also occur in association with certain deficiencies of the pituitary thyroid or adrenal glands and functional or organic disturbances of the nervous system A typical history of hyperinsulinism is illustrated in the first case ever reported

A physician 40 was admitted with symptoms of 18 months duration including attacks of faintness and weakness associated with numbness of tongue and lips and later with profuse perspiration and trembling The attacks came when meals were delayed or if unusual exertion was undertaken and could be avoided by eating between meals He had two more severe attacks during one of which he fell in a stupor and was revived when given an eggnog the second episode was that of coma following a short period of fasting and resuscitation was effected by intravenous injection of dextrose Clinical and laboratory tests on admission confirmed the diagnosis of hyperinsulinism Exploratory operation and autopsy one month later, revealed carcinomatous tumor of the tail of the pancreas and metastasis to the liver

This case demonstrates the importance of early operation in the presence of adenomas of the island cells of the pancreas because some such tumors are definitely malignant When a single adenoma is present its removal results in cure occasionally there are several adenomas When a hyperfunctioning adenoma is not found resection of portions of the pancreas gives varying results which are often disappointing There is no method available for preoperative diagnosis of hyperfunctioning tumor of the pancreas There is no method

(4) Rocky M unt 1 M J 39 343 345 M y 1942

for the assay of insulin in the circulating blood Sugar tolerance tests and determinations of blood sugar values following various diets have not been of help An exploratory operation should be performed on any patient whose symptoms are severe and whose story is true According to Whipple these cases should fulfil the following criteria (1) normal health and evidence of stability of the autonomic nervous system prior to the first episode of hypoglycemia (2) absorptive levels of blood sugar of less than 0 06 Gm per 100 cc and (3) intolerance of fasting

Keating and Wilder in discussing the differential diagnosis of true hyperinsulinism and nervous hypoglycemia stated that the latter is hypoglycemia associated with functional neurosis or a hyperirritable autonomic nervous system The patient is unstable emotionally He complains of hunger and weakness before meals and may faint on occasion but regains consciousness without treatment Especially notable is absence of symptoms at night values for sugar after a night s fast are not abnormally low and the symptoms and low levels of blood sugar are related more to ingestion than withdrawal of food The hypoglycemic phase of the blood sugar time curve of the dextrose tolerance test is abnormally low It is suggested that the disturbance in such subjects lies not in abnormality of carbohydrate metabolism but in abnormal sensitivity of the individual to physiologic excursions of the blood sugar level Moderate activity of healthy persons may cause depression of the blood sugar to low normal or even hypoglycemic levels with or without mild symptoms of hypoglycemia Just as the nervous person over reacts to pain and other stimuli he also over reacts to the level of sugar in the blood

Specific Gravity of Healthy Men Body Weight Divided by Volume as Index of Obesity A R Behnke Jr B G Feen and W C Welham[5] (Washington D C)

(5) J A M A 118 495 498 F b 14 1942

report that the fundamental biologic characteristic of corporeal density can be accurately measured usually *within 0 004 unit by the method of hydrostatic weighing* provided a correction is made for the air in the lungs Values of specific gravity for healthy men ranging in age between 20 and 40 fall between 1 021 and 1 097 An example illustrating the method of computing specific gravity is given in the table Low values for specific

		Lb	Kg
Weight of the body in air		183 00	83 20
Weight in water full inspiration		14 70	6 45
Weight in water complete expiration		23 20	10 55
Vital capacity computed from the volume of water displaced	4 090 cc		
Vital capacity by spirometric measurements	*4 150 cc*		
Volume of residual air	1 200 cc		
Weight of abdominal belt		13 75	6 25
Corrections			
Gross weight in water		23 20	10 55
Weight of belt		13 75	6 25
Weight in water not corrected for residual air		9 45	4 30
Correction for residual air (1 200/453)		2 65	1 20
Net weight in water		12 10	5 50

$$\text{Specific gravity} = \frac{\text{Weight}}{\text{Volume}} - \frac{183}{170\ 9} = 1\ 071$$

gravity *indicate obesity and conversely high* values denote leanness Individual loss in weight through exercise and a restricted diet is associated with an increase in specific gravity Difference in the circumferential *measurements of chest and abdomen serve as a criterion* of obesity and can be correlated with specific gravity Variation in the percentage of bone in relation to body weight excluding excess fat is not expected to produce *deviation of more than* 0 013 *units in comparable values*

A further examination by W C Welham and A R Behnke Jr [6] of exceptional athletes and of naval personnel in which the body weight divided by th volume

(6) *J A M A* 118 498 501 Feb 14 194

and other physical characteristics were especially considered showed that 17 of 25 athletes could be considered not physically qualified for military duty or first class insurance risk on the basis of the standard height weight tables used by insurance companies and in the military service even if an allowance of 15 per cent above the average values in the tables is considered as the upper limit Of the 17 all American football players 11 fell into the group possessing high corporeal specific gravity According to the authors classification these 11 men are in prime physical condition if absence of excess fat is a criterion of fitness The type of physical exertion moreover that these men are called on to make is proof of their sturdy physique estimated in terms of speed agility and endurance The authors propose therefore the classification of men as overweight on the basis of specific gravity of the body mass using a tentative dividing line of 1 060 for elimination of the obese This division is diametrically opposed to a division based on height weight tables

Acute Porphyria may be classified as acute toxic and acute idiopathic porphyria Samuel Nesbitt (Yale Univ) and Charles H Watkins (Mayo Clinic) consider these two as probably one condition and state that both should be included under acute porphyria which is caused by an inborn error of porphyrin metabolism The condition is characterized by gastro intestinal disturbances and involvement of the central nervous system There may or may not be fever Commonly there is severe abdominal pain which may be generalized or confined to the lower part of the abdomen There may be nausea vomiting constipation and ileus there may also be mild jaundice There is occasionally a diffuse or spotted pigmentation of the skin but not of the mucosa the nature of this pigmentation is unknown Involvement of the central nervous system is exhibited most frequently by an ascending type of paralysis and death

(7) Am J M Sc 203 74 83 J u ry 1942

is frequently due to bulbar involvement with respiratory failure There are frequently delirium and hallucinations Photosensitivity occurs rarely Patients with acute porphyria usually excrete uroporphyrins III and I in the urine with great predominance of the type III isomer Uroporphyrin has not been demonstrated in the feces of such patients which usually contain only a small amount of coproporphyrin III It was shown recently that uroporphyrin may be excreted as a metal complex and between the acute episodes the fraction of uroporphyrin which is present as a metal complex may be increased Usually only a relatively small amount of coproporphyrin III is present in the urine Other pigments apparently are involved in this metabolic disorder Pigments other than porphyrins may account for most or all of the characteristic dark color of the urine Various workers claimed that urofuscein pigments made up of several united pyrrole nuclei skatol red or urobilin may constitute most of the color of the urine of these patients

Three cases are reported in which diagnosis was confirmed by demonstration of large quantities of uroporphyrin in the urine most of which was of isomeric series III there being a small fraction only of uroporphyrin I Spectroscopic examination showed that this occurred as the zinc metal complex Another case is reported which presented the usual clinical picture of acute porphyria but which was diagnosed as paroxysmal hemoglobinuria on the basis of spectroscopic studies which demonstrated oxyhemoglobin in both urine and blood serum during crises The authors suggest that this case actually represents one of acute porphyria and that the absorption bands which were observed and believed to be those of oxyhemoglobin were probably those bands of zinc metal complex of uroporphyrin The error might be explained easily since oxyhemoglobin produces absorption bands at 585 to 567 mμ and 550 7 to 527 mμ with maximal absorption which corresponds almost precisely with the

bands of uroporphyrin zinc metal complex at 577 and 541 mμ respectively The bands of uroporphyrin zinc metal complex are distinguished only by the fact that *when a little concentrated hydrochloric acid is added* the complex is broken up and the bands are replaced immediately by those of uroporphyrin

This disease entity is not as unusual as has formerly *been supposed and with a more general knowledge of* the subject more cases will be detected

Water Deficiency in General Practice R H Micks[8] (Dublin) states that knowledge of dehydration by the general practitioner is of utmost importance even though *most patients in a state of dehydration* will be sent to a hospital Intelligent anticipation based on proper knowledge may prevent the last stages of dehydration When sulfapyridine administration has to be pushed to the extent of causing vomiting measures to combat dehydration may be required at an early stage A special reason for parenteral administration of saline to patients vomiting as result of sulfapyridine is found in the importance of maintaining a high output of urine to prevent deposition of crystals of the acetyl compound in the urine and eventual serious renal damage

Infantile diarrhea rapidly produces collapse and in such cases the only satisfactory route may be intravenous *injection a matter for experts There is no easy way* of administering fluids to a badly dehydrated infant in the home and the practitioner who saves most infants with diarrhea *will be he who anticipates the need for* special treatment by sending his patients at an early stage to a properly equipped children s hospital

Treatment of diabetic coma in the home requires a large amount of insulin saline solution a stomach pump and finally the resolution by the patient not to leave the house until recovery has begun

Intravenous infusion is necessary only when circula

(8) P t t 148 1 1 6 Ap 1 194

tory failure has appeared or when as in cholera no other method is feasible The rectal route is the one of choice if rapid absorption of a large volume is not required, diarrhea contradicts this route The subcutaneous route is not adequate for rapid administration of large volumes of fluid nor does the intramuscular route permit the rapid administration possible by the intravenous route On the whole normal saline is adequate in every case Glucose and saline are often given but glucose does not appear to be required except in hypoglycemia Alkalinizing fluids such as sodium bicarbonate and sodium lactate solutions are used in acidosis Acidosis with hyperpnea often accompanies dehydration being particularly common in diabetic ketosis but treatment by normal saline is effective (with insulin in diabetes) Interstitial fluids are unnecessary except in rare cases in which deficiency of calcium or potassium compounds in addition to sodium chloride exists

Comparison between Dehydration from Salt Loss and from Water Deprivation Joseph W Nadal, Svend Pedersen and Walter G Maddock[9] (Univ of Michigan) discuss the two distinct types of dehydration, which depend on whether the condition is associated with (1) a primary loss of salt or (2) a shortage of water not accompanied by a corresponding loss of salt The former is characterized by circulatory disturbances and the latter by thirst In animals dehydrated by loss of salt the principal loss of fluid is from the extracellular portion including the blood whereas in thirsting animals the water loss is distributed among all fluid compartments of the body including the large intracellular portion Most physicians have not been sufficiently aware of this important distinction and its therapeutic implications The authors present a study of these two types of dehydration in normal human subjects Results indicate that the two types differ from each other in mechanism of production in manifestations and in treatment indi

(9) J Cl I estigat n 20 691 703 No mber 1941

cated and are quite comparable to experiments with rabbits which have been described by Kerpel Fronius

Dehydration resulting from simple water deprivation is characterized by thirst and oliguria does not lead to impairment of the circulation and is completely relieved by administration of water Dehydration resulting from abnormal salt loss results mainly in a loss of extracellular fluid a reduction in plasma volume and disturbances in the circulation It is neither characterized by thirst nor relieved by administration of salt free fluids but is promptly relieved by fluid containing sodium chloride A detailed study was made of the balances of energy water sodium and potassium during a period of total fasting and recovery The results indicate that during dehydration and recovery the balances of sodium and potassium do not necessarily correspond to the water balance over short periods

Newer Studies on Pellagra are presented by G Frontali[1] (Padua Italy) Addition of nicotinic acid or nicotinic acid amide to a pellagrogenic diet transforms it into a pellagra preventive or pellagra curing diet The pronounced effect of such treatment is manifested not only in rapid disappearance of the skin mucous membrane capillary and gastro intestinal symptoms of hypochlorhydria and hypochlorhydric reaction and of all nervous and psychoneurotic symptoms but also in restoration of nitrogen balance increased metabolic rate and decreased porphyrin and marked increase in nicotinic acid output in the urine

These results prove that human pellagra is not a composite syndrome a mosaic like deficiency disease but a clinical etiologic and pathogenic entity The symptoms of nicotinic acid deficiency or near deficiency states may appear as various dystrophies especially in infantile and nontropical sprue Further studies are necessary for complete clarification of the nicotinic acid metabolism The addition of nicotinic acid to a diet

(1) Sch m d W h sch 2 208 17 F b 1 1942

deficient in meat may aid in solving the nutritional problems which will arise during the present war

Dietary Protein and Regeneration of Serum Albumin

A A Weech (Columbia Univ) discusses the potency values of dried beef serum whole egg cow s milk cow s colostrum lactalbumin and wheat gluten and reviews a method of assaying various food proteins for efficiency in promoting the formation of serum albumin He presents the results of 75 assay experiments which lead to the establishment of potency values for six food proteins

Dried beef serum with a potency value of 0 739 is a superior protein for producing serum albumin synthesis The value is not significantly different from that of 0 801, previously obtained in assays of fresh beef serum Whole egg with a potency value of 0 602 is a good protein for inducing serum albumin synthesis The value is almost identical with that of 0 616 previously obtained in assays of egg white Cow s milk with a potency value of 0 485 is fairly well utilized for the formation of serum albumin The result is somewhat not significantly higher than the value 0 388 previously obtained in assays of casein Cow s colostrum with a potency value of 0 611 appears to furnish good protein for forming serum albumin Only nine assays were made and the result is less reliable than with most of the other foods The value is about what would be expected if the protein of colostrum were a mixture of the proteins of milk and beef serum Lactalbumin with a potency value of 0 773 is a superior protein for inducing synthesis of serum albumin There is no evidence that it differs in effectiveness from either fresh or dried beef serum but superiority over egg protein can be demonstrated Support for the high rating given to lactalbumin was found in an additional experiment in which the feeding of this protein at the standard level brought about in 26 days an increase in albumin concentration in the serum from

( ) Bull. J h Hopki s H p 0 15 1 6 [illegible] 1942

1 31 Gm per cent to 4 06 Gm per cent Wheat gluten with a potency value of 0 207 is a poor protein for producing serum albumin formation

The relative effectiveness of these six foods and of the six foods previously reported on (fresh beef serum egg white beef muscle beef liver casein and gelatin) is evaluated by conventional statistical procedures Fresh beef serum has the highest potency value whereas gelatin has the lowest potency value

[The recognition and correction of hypoproteinemia and its sequelae are assuming greater importance in clinical medicine Therefore any preparation of promise whether given orally or parenterally is decidedly welcome The latter procedure is useful in patients who are too ill to partake of nourishment by mouth and in whom a rapid building up of the blood proteins is essential Heretofore preparations of amino acids for intravenous administration left much to be desired However following extensive investigation in this country especially at Wayne University a product suitable for parenteral administration appears to have been prepared. Clark and Brunschwig (134) report the successful intravenous administration of solutions consisting of mixtures of 10 per cent enzymatic hydrolysate of casein with 5 or 10 per cent dextrose in distilled water with added fat emulsions in certain cases —Ed.]

Treatment of Hypoproteinemia by Oral Administration of Protein Hydrolysate C Abbott Beling and Robert E Lee[3] (St Barnabas Hosp Newark N J) discuss methods of replacement or restoration of the proteins in the plasma and the body s general store of proteins Oral administration of amino acids or immediate precursors of these appeared theoretically particularly promising since amino acids are rapidly absorbed from the gastro-intestinal tract essential amino acids introduced into the upper jejunum should be promptly absorbed Pure amino acids were found to be unsuitable because of expense impurities and their capacity to cause irritations An enzymatic hydrolysate of proteins from beef wheat and milk was used from this mixture an adequate amount of each of the essential amino acids including methionine is obtained

(3) A h S g 43 735 747 N mb 1941

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( ) Bull J h H pk ns H p 0 15 1 C F b y 1942

alysis of the other cases shows that the speed of replacement is rapid but not fast enough for treatment of shock and immediate hypoproteinemia The hydrolysate is valuable as an adjunct to intravenously administered plasma The preoperative and postoperative use of such a protein hydrolysate in gastro-intestinal surgical procedures is important to correct hypoproteinemia before operation and to prevent its occurrence afterward

Administration of the protein hydrolysate by an indwelling tube in the duodenum or jejunum was well tolerated The continuous drip method is simple and requires no more than the ordinary set for administering fluids intravenously There should be a drip chamber in the line for adjustment of rate of flow The 25 per cent solution of the hydrolysate is poured into the flask and the drip adjusted to a flow of about 80 drops per minute *Occasionally it is necessary to flush the tube with physio*logic solution of sodium chloride or water

Genesis of Pellagra Pernicious Anemia and Sprue The investigations conducted by Seale Harris and Seale Harris Jr[5] (Birmingham Ala) show that pellagra pernicious anemia and sprue are distinct disease entities The oral and gastro-intestinal symptoms in pellagra without skin lesions pernicious anemia and sprue may be indistinguishable in cases in which there is macrocytic anemia The most effective treatment in these diseases is liver and liver extracts of which nicotinic acid is an ingredient Disease of the liver usually fatty degeneration is an almost constant finding in pellagra and pernicious anemia and to a less extent in sprue Atrophy of the stomach and intestines may be found in all three diseases If spinal cord changes are found in either of the three the lateral and posterior columns are involved Liver insufficiency seems to be a factor in the genesis of the three conditions Cases are reported in which pellagra and pernicious anemia sprue and pernicious anemia and pellagra sprue and

(5) Am J Dg t D 9 93 J ry 1942

This hydrolysate was given to 30 patients, either orally or by an indwelling tube It produced satisfactory replacement of proteins in the plasma and correction of the various anomalies which accompany hypoproteinemia One case was particularly instructive because of profound hypoproteinemia and inability of the patient to tolerate ordinary forms of nourishment With

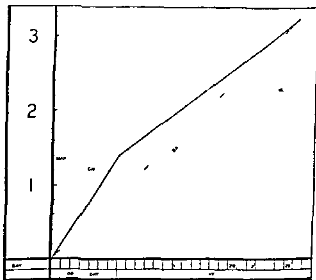


Fig 176—Mean daily increase of proteins in blood plasma of 25 patients treated with 1½ oz protein hydrolysate daily

daily administration of 2 drachms of the protein hydrolysate, the proteins in the plasma were increased from 2 9 to 5 08 Gm per 100 cc in one week the average daily increment was thus 0 3 Gm Simultaneously, the proteins in the plasma rose to 7 4 Gm at the end of 15 days The patient received corn syrup and goat s milk alone for some days but the proteins fell steadily until edema reappeared a little before they reached a level of 5 6 Gm Resumption of the protein hydrolysate feeding promptly corrected the condition a second time An

developed them during and notwithstanding treatment

Despite the comparatively limited and modest results which aged people might expect from treatment with vitamins it seems clear that in suitable cases the relief obtained in some pathologic senile features might be considerable The results obtained provide strong support to the argument repeatedly emphasized by authorities in modern nutrition that the greatest care should be taken to prevent occurrence of partial or latent vitamin deficiency apparently widely spread in the population This will result not only in prevention of certain vitamin deficiency diseases but probably also in the approach to a less pathologic senility

Nutrition Study in Pregnancy Philip F Williams and Florence G Fralin[8] (Philadelphia Gen'l Hosp) present dietary analyses of seven day food intake records of 514 pregnant women comparison of actual food intakes with variously stated requirements and relationship of food intake to various obstetric factors Only 10 of the diets could be termed good 209 fair and 295 poor The diets fell much below the standard in all elements when compared with the recommended dietary allowances of the National Research Council Caloric *carbohydrate and fat intakes were found to* be unaffected by income The intake of vitamin A vitamin B_1 ascorbic acid and riboflavin rose with the income Protein calcium and iron showed a slight rise with increased income The group did not show any positive relationship between dietary adequacy and the occurrence of certain complications of pregnancy and child birth *There was no evidence that toxemia occurs* in the presence of insufficient protein vitamin A or vitamin B_1 intake There were not enough cases of abortion hemorrhage pyelitis and cystitis and intercurrent infection to justify any conclusions. Protein deficiency did not seem responsible for the production of premature labor in a small series of cases The same

(8) *Am J Obst & Gynec 43 1 20 January 1942*

pernicious anemia existed in the same patients, thus suggesting common etiologic factors The frequency of intestinal parasites in anemic patients with pellagra, pernicious anemia or sprue possibly suggests that intestinal toxemia and liver insufficiency may be etiologic factors in some cases The occurrence of pellagra in alcoholics and the not infrequent complication of pernicious anemia in cirrhosis of the liver suggest that liver disease and/or liver insufficiency may be factors in alcoholic pellagra and pernicious anemia in patients with cirrhosis of the liver Pellagra, pernicious anemia and sprue appear to be allied nutritional diseases

Some Effects of Vitamins B and C on Senile Patients W Stephenson C Penton and V Korenchevsky[6] (Oxford Univ) treated 40 senile patients with vitamins B complex and C and observed them for about a year Their condition was compared with that of 18 senile controls receiving dummy tablets All patients were on a usual hospital diet not rich in vitamins

Treatment with vitamins B and C did not stop the biologically inevitable development of senility and therefore did not affect those basic features which are specific for and present in even the most physiologic type of senility It was possible however to prevent or improve sometimes strikingly certain of those senile features which can be considered as pathologic because they appear prematurely or in an extreme degree these features include muscular cardiovascular and mental deterioration and some features which do not seem to be inevitable in normal physiologic senility such as dementia, insomnia skin rashes and itchings and constipation During the period of observation improvement or disappearance (apparently not of lasting nature) of some pathologic senile features was observed in numerous cases while in a number of others there was no improvement on treatment and a few patients previously free from certain senile features

(6) Brit M J 859 844 Dec 13 1941

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(8) Am J Ob t & Gy 43 1 20 J ry 194

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(6) Brit M J 2 839 844 Dec 13 1941

to be eating much less raw fruit and less unrationed meat fish and sweets and chocolates than the women surveyed in 1935 Milk bread and other cereal foods potatoes and other vegetables were being consumed in larger amounts in the 1941 survey

The women in the 1941 survey had maintained their calories at their prewar level by substituting unrationed carbohydrate for rationed fat Their protein and phosphorus intakes were unchanged their calcium and iron intakes were higher than they had been in 1935 The amount of animal protein was less in the wartime dietary The average vitamin C intake was 57 mg a day *in 1935 and 27 mg in 1941 This decrease* was due entirely to the disappearance of raw fruit from the market Three fourths of the women in the 1941 survey were having less than 30 mg a day The vitamin C intake in wartime must be expected to vary from one season to another as it has ceased to do in peacetime The survey was carried out in the lean season no doubt the intake of vitamin C would have been much higher in the summer and autumn

The general results indicated that people were eating smaller amounts of a great many foods in 1941 but that rationing of some foods brought about larger consumption of a number of unrationed foods

Obesity in Childhood I P Bronstein S Wexler *A W Brown and L J Halpern*[1] *(Univ of Illinois)* studied 35 children whose obesity could not be attributed to ascertainable endocrinologic disturbances The mean intelligence of this group was above the mean of the population as a whole There seemed to be a tendency for the children to fall into two classes superior and retarded almost 50 per cent were above average and 25 per cent below As far as can be determined from achievement tests these children showed little or no difference from children of similar capacity Of 24 boys only 2 showed a tendency toward feminity Thus

(1) Am J Dis Child 63 38 1 Feb y 194

may be said for vitamin A The number of neonatal deaths and stillbirths was too small to show any positive relationship to dietary inadequacy The diets of those women who were morbid after delivery did not differ markedly from the remainder of the group with respect to protein vitamin A or vitamin C intake Protein intake apparently had no bearing on the ability of the women to nurse their babies during the hospital stay

An intake below the pregnancy standard of 600 units of vitamin B was found in 84 per cent of a group who presented a history of nausea and vomiting in early pregnancy An apparently normal reproductive process was present in 250 women in the series Their food intake showed no variation from that of the entire group of 514

Middle Class Diets in Peace and War The restrictions and alterations in established dietary practices caused by the war have *according to E M Widdowson* and B K Alington[9] (Cambridge Univ) raised a number of important questions To what extent was the rationing really a restriction? Was the apparent scarcity of an unrationed food due to increased demand or to decreased supply? If the consumption of some commodities was curtailed were people eating less food or were they turning to other more plentiful foods? To obtain answers to these questions the records of a dietary survey carried out in 1935 on 63 men and 63 women of the English middle class were reanalyzed At that time the men were eating an average of twice as much sugar and bacon three times as much meat butter and jam and five times as much cheese as was allowed them in the spring of 1941 The women were eating less of these foods but the quantities of all of them except sugar exceeded their rations in the spring of 1941 An individual dietary survey was carried out in the spring of 1941 on 57 women of a similar social class They were found

(9) La et 361 365 Sept 27 1941

another 2o per cent from families with more than two children In the absence of any physical defects the adiposity of these children was probably contributed to by their sedentary habits abnormal appetites par ental attitudes and other environmental factors

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with the Terman Miles test this group showed no greater tendency toward feminity than might be expected in any comparable group *This is contrary to* the view held by many investigators

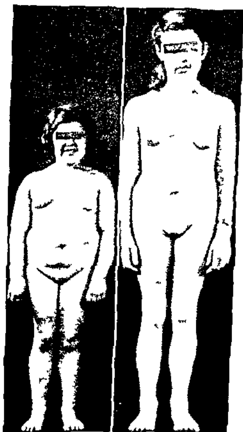


Fig 177 (left) —Patient t 8 years
Fig 1 8 (right) —S m pat e t 11 po t neous or ect ft r th ye

The "aspects of personality *test indicated* that the children were no different from other children as far as ascendancy submission was concerned but that they had a tendency toward extroversion and instability There was a definite tendency for the children to be sensitive about their obesity Most children were reported to be interested in sedentary play activities such *as going to the* movies listening to the radio and reading No known history of obesity in most of the parents or siblings of these children could be found Fifty per cent of the patients came from families with two children 25 per cent from families with one child and

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